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A Review of Chronic Kidney Disease Due to Unknown Etiology and Groundwater Quality in Dry Zone , Sri Lanka

[Charuni Wijerathne[1], S.K. Weragoda[2], Tomonori Kawakami[3]]

***Abstract*— Chronic Kidney Disease due to unknown etiology (CKDu) is a deadly disease of which the prevalence have been identified in several countries in North Central America, India and Sri Lanka. Several studies have showed that, the usual factors as long-standing diabetes and hypertension are not the leading causes for the majority of CKD patients from the dry zone of Sri Lanka. Many researchers suggest that the etiology for CKDu may be a combination of several environmental factors. Some suggest that even though no single geochemical parameter could be clearly and directly related to the CKD etiology, it is very likely that the unique hydro-geochemistry of the drinking water is closely associated with the incidence of the disease. Hence this research was aimed to identify the CKDu prevalence in Sri Lanka and the similarities with the reported cases in the world, and to evaluate the suggested etiologies for the CKDu in Sri Lanka with more focus to the strong etiology suggestions. Initially a thorough literature review was conducted to identify the existing hypothesis and analyzed published and unpublished data to define strong hypothesis related to groundwater quality, socio-economic and environmental facts. Also, a field groundwater quality investigation was conducted in several endemic and non-endemic regions. The results showed that some of the risk factors in Sri Lanka are similar to other country cases, and mainly the excess fluoride and hardness levels seems to have a direct impact on the prevalence of CKDu in Sri Lanka. However, no any heavy metal has proven for direct correlation with the CKDu prevalence.**

Keywords*— CKDu, Etiology, Groundwater Quality, Fluoride, Hardness*

I. Introduction

Ground water (GW) is the main source of drinking water in many rural communities in Sri Lanka. As per National Water Supply & Drainage Board data in 2012, population covered with pipe borne water coverage in many provinces are less than 40% except Western & Southern provinces. It is evident with several studies done in recent past that there is an increasing trend on the reporting of patients admitted with Chronic Kidney Disease due to Uncertain etiology (CKDu) (Bandara et al, 2008; Chandrajith et al, 2010). It is found that nearly 87% of the population in the Anuradhapura administrative district in the north central region where most areas are affected by CKDu use either dug well or tube well water (Perera et al. 2008 cited in Chandrajith et al., 2010).

Over one thousand people have been reported as dead due to CKDu and more than 35,000 patients have registered at renal clinics of several government hospitals in the dry zone of the island (Weragoda et al., 2013a). From many studies, it has been clearly showed that the etiology behind the increased number of CKD patients in NCP, is neither diabetes nor hypertension (Bandara et al., 2008). Etiology for this mysterious disease is suggested to be a combination of several environmental factors. Chandrajith (2010) suggests that even though no single geochemical parameter could be clearly and directly related to the CKD etiology, it is very likely that the unique hydrogeochemistry of the drinking water is closely associated with the incidence of the disease. Also many studies stresses the specialty of the spatial distribution of this disease, which is highly associated to the North central dry zone of the country. Hence this study focused at identification of the similarities between the national and international CKDu types, to narrow down the risk factors and also to analyse the groundwater quality in several CKDu endemic and non-endemic regions to evaluate the relation of groundwater quality with CKDu prevalence in dry zone, Sri Lanka.

II. Groundwater Quality Survey

The groundwater quality survey was conducted in three endemic CKDu regions of Anuradhapura (n = 186), Polonnaruwa (n = 56), Badulla (n = 65) and three non-endemic regions Batticaloa (n = 30), Kandy (n = 25) & Hambantota (n = 142). Mainly 6 water quality parameters were measured in all five districts while 17 additional parameters were tested in Anuradhapura, Polonnaruwa, Hambantota and Batticaloa. The spatial variation of the water quality parameters were evaluated to identify any relation among CKDu and groundwater quality. The standard sampling and analytical methodologies were followed throughout the study (APHA 1998).

The fluoride content in water samples were measured using Chromatographer Fluoride Meters and the trace metals detection including Cadmium were performed by inductively coupled plasma mass spectrometry (ICP-MS) at the Toyoma Prefectural 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.

[1] Lecturer, Department of Civil Engineering, International College of Business & Technology, Mount Lavinia, Sri Lanka

[2] Chief Engineer, National Water Supply and Drainage Board, Sri Lanka

[3] Senior Professor, Dept. of Environmental Engineering, Faculty of Engineering, Toyama Prefectural University, Japan

III. Etiology for CKDu

According to National Kidney Foundation, USA (2002) CKD is recognized as a common condition that elevates the risk of cardiovascular disease as well as kidney failure and other complications and this disease is found to be prevailing rapidly in worldwide due to the increase in the prevalence of obesity, diabetes and hypertension, the leading risk factors for CKD. Several studies have showed that, unlike in other countries where long-standing diabetes and hypertension are the leading causes of CKD, the majority of CKD patients from the dry zone of Sri Lanka do not show any identifiable cause. Many researchers suggest that the etiology for this mysterious disease may be a combination of several environmental factors.

Chandrajith et al. (2010) suggests that even though no single geochemical parameter could be clearly and directly related to the CKD etiology, it is very likely that the unique hydrogeochemistry of the drinking water is closely associated with the incidence of the disease.

A. *What are the other countries who had similar kind of an issue?*

There are several studies done in worldwide regarding CKD prevalence and its prevention but very few studies have been done on CKDu in other countries which may be due to poor documentation (Athuraliya et al., 2009). According to Jha, et al. (2013) there are several countries including Malaysia, Italy, Austria, Argentina, UK etc. that reports about CKD due to unknown etiologies and except Sudan and Nigereia all other countries report, that less than 30% of the CKD population is due to unknown reasons. In Sri Lanka the percentage varies drastically from region to region. But when it is considered as a percentage for the country, the effect of CKDu may not be visible. This might be the cause for the lower parentages reported in other countries under CKDu. Somehow, the studies done on these kind of health problems are very few and also incomparable in some aspects due to many reasons such as differences of environmental facts, environmental pollution, pesticides, analgesicabuse, herbal medications, use of unregulated food additives and genetic factors etc. which can contribute to the burden of chronic kidney disease in developing countries (Jha, et al., 2013).

Also as stated by Jha, et al. (2013), USA has reported a very lower percentage of CKDu patients when considers the average of all the regions. But many researches show that there is a significant problem of CKD due to an unknown etiology even in North Central America, with higher number of cases reported. But when it comes to the average, the significance of the problem has been hidden.
This includes Balkan Countries such as Bulgaria, Romania, Serbia, etc. in Southern Europe, some countries in North Central America such as El Salvador, Mexico & Nicaragua, also Asian countries such as India, Sri Lanka, China & Taiwan and also some countries in Africa such as Congo, Egypt, Morocco, Senegal, Nigeria, Libya, Burkina Faso, Tunisia & Sudan, etc. Even from these, in the African countries still the discussion on the significant amount of CKDu patients is not much evident. The discussions regarding the existence of the broader spectrum of histopathological lesions in HIV-associated kidney disease in African populations seems to be given priority. Especially when consider the geographical distribution of the reported CKDu issues around the world such as, Balkan region in Southern Europe, El-Salvador and Nicaragua and surrounding regions in North Central America, and also in Asian countries like India, Sri Lanka, China and Taiwan, the problem seems to be evident in tropical & sub-tropical countries in the world . According to El-Minshawy (2011), in El-Minia, Egypt which is an African country, the etiology of End Stage Renal Disease (ESRD) was unknown in 27% while in the USA it is only 3.7% of the patients. Also from the reported 27%, 25% is from rural areas while just 2% have been reported from urban areas, which stresses another similarity in the CKDu cases found in other countries.

B. *CKDu in Balkan Region*

Balkan endemic nephropathy (BEN), also known as Danubian endemic familial nephropathy, is a chronic kidney disease that affects the kidney interstitium leading to fibrosis and decreased kidney function. BEN was first identified in the 1920s among several small, discrete communities living along the confluence of the Danube River of Croatia, Bosnia and Herzegovina, Serbia, Romania and Bulgaria. These regions of plains and low hills generally have high humidity and rainfall. But, in Sri Lanka the issue is in the dry zone and since the disease type has some deviations with the facts here, it is difficult to inter-relate the findings of those studies with this. Also, BEN and the Chinese herbs nephropathy (CHN) are chronic tubulointerstitial renal diseases associated with urothelial carcinoma. According to him, the clinical expression and pathological lesions observed at different stages of CHN and BEN are strikingly similar. To date, the most believed etiology for BEN seems to be the exposure to aristolochic acid (AA), a powerful nephrotoxin and human carcinogen and also suggests to abandon the terms ‘ CHN ’ and ‘ BEN ’ and introduce ‘ aristolochic acid nephropathy ’ to cover both clinical conditions.

C. *CKDu North Central America*

According to the past and ongoing studies, high prevalence of CKDu can be seen mainly in El-Salvador and Nicaragua. The disease recently named as Mesoamerican Nephropathy (MeN) and in El-Salvador, the kidney disease has become the second leading cause of death among adult men. Across the region, kidney failure has killed more than 2,800 men each year from 2005 to 2009, according to an analysis of data from the WHO (Chavkin, 2012a).

1) Etiology for CKDu in El-Salvador

Studies in El-Salvador suggests that the unknown cause is associated with neither diabetes nor hypertension and associations were found with age, male sex, hypertension and family history of chronic kidney disease, with decline in kidney function beginning at early ages. Furthermore, the male farmers have a dual burden of non-traditional (occupational, toxic environmental) and traditional (vascular) risk factors that could act in synergy, contributing to kidney damage.

2) Etiology for CKDu in Nicaragua

There are many suggested hypothesis for the cause of this epidemic, and it is supposed to be linked to multi-factorial dietary, environmental, and occupational exposures. Further this study has identified a difference of the prevalence pattern subsistence in farming/mining village and the banana/sugarcane growing village. Also the lowest rates were seen in two villages with service industry and coffee-growing economies. Also, it has shown that more llikely etiology fir this as, Heat stress and dehydration (including electrolyte imbalances) and Non-steroidal anti-inflammatory drugs (NSAIDS).

D. *CKDu in Asian countries*

In Asian countries, where traditional medicines are very popular and pharmaceutical medicines are frequently substituted or supplemented by botanical products that include herbs containing aristolochic acid, High CKD prevalence has been identified. Also the epidemiological data from Taiwan and China show an association between the use of herbs containing Aristolochic acid and CKD (Guh, et al., 2007).

1) Etiology for CKDu in India

India is one of the three major countries where CKDu prevalence has taken attention around the world. The epidemics affect sharply defined geographic areas that are stunningly fertile and swelteringly hot. The victims mostly conduct heavy manual labor, have little formal education and lack easy access to medical care. Pesticides are used heavily, and communities drink local groundwater (Chavkin, 2012b). Hence above causes are considered to be in the main hypothesis for many investigations and also from a study conducted in Srikakulam district of India, no excess of heavy metals were found in the water (Jha, et al., 2013). Hence, the remaining hypothesis for India show quite a strong similarity between those discussed for North Central America.

2) Etiology for CKDu in Sri Lanka

This issue appeared in Sri Lanka in early nineties and then the incidence of the disease amplified gradually reaching high numbers in 2002. The majority of the CKDu patients in North Central Province are from low socioeconomic farming community (Jayatilake, et al., 2014). Many Risk factors from different studies are currently under discussion, and many suggests this as a multifactorial caused disease (Bandara et al., 2008). Among the risk factors there were: source of drinking water (agro-well, tube well, or garden well); habits (alcohol consumption, smoking, or betel chewing); family history of CKD, and history of snake bites; frequently used medication; and parental consanguinity. Also since 2009, the Health Ministry and WHO had embarked on the world's largest and most comprehensive study of CKDu. Main hypothesis was related with the possibility of heavy metals existence in food, water and soil in dry zone. In June 2012, the Health Ministry and WHO publicly identified chemicals which were mentioned were an essential cause of the disease: The heavy metals cadmium and arsenic, through low-level exposure likely occurring through the food chain. But according to Weragoda, et al., (2013a) the concentrations of Cadmium, Lead, Zinc and Chrome were lower than the Sri Lankan standard as well as WHO guideline in most of the regions in dry zone of Sri Lanka. Also a study by Bandara et al. (2008) presents supportive finding for the Cd existence in diets while Chandrajith, et al., (2010) discusses some opposite findings to the Cd related hypothesis. Recent studies show a relation between the regions with high fluoride levels and the CKDu prevalent regions (Weragoda et al., 2012, Bandara et al., 2008). Another important risk factor is use of Al utensils for cooking (Illeperuma, et al., 2009). Especially 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, which if used with acidic conditions which is a traditional cooking practice, the situation gets even worse. Aluminum fluoride is very poorly excreted in the urine and it is poisonous to the kidneys. However, no comparison has been done in the study by Illeperuma et al. (2009) with the non-endemic regions.

3) Fluoride in groundwater in dry zone, Sri Lanka

However, recent studies have found that there is a strong linkage between the drinking water quality & the amount of water. Especially with the unpublished data by Weragoda et al. (2013), strongly suggest that the prevalence of CKDu found to be less in the areas with the water supply from National Water Supply and Drainage Board. Further they have found that CKDu patients in stage 1 & 2, could be cured with the use of properly treated drinking water. But along with this finding, they have seen a contradictory change in the effect for the families who use the same well for drinking water, which gives rise again to other hypothesis unrelated to drinking water.

When consider the distribution pattern of fluoride concentration in the groundwater of Sri Lanka, it is quite visible that the higher concentration areas overlaps with the

CKDu reported zones (Nagasawa et al., 2013). The WHO specifies that the upper limit of F- concentration is as 1.5 mg/l and for Sri Lanka, as a country in the tropical region the upper limit value is as 0.6 mg/l (Warnakulasuriya et al., 1992 cited in Chandrajith et al., 2010). When consider the groundwater F- concentration distribution in Sri Lanka in most cases it exceeded this limit. This has been proved by several studies done in past decade and also through a recent study done by Weragoda, et al., (2013b) and also is considered to have a strong impact on the CKDu. However there's a huge requirement of a community level sustainable solution for groundwater treatment which is suitable for the dry zone in Sri Lanka.

E. *Groundwater Quality Survey*

1) Excessive Fluoride

Excessive fluoride amounts cause critical health issues such as dental caries, bone fluorosis, and lesions of the thyroid, endocrine glands, and brain. This problem has wide spread in many parts of the world, and still many millions of people consume groundwater with high amounts of fluoride which exceeds the recommended guideline value by World Health Organization (WHO). As a country in the tropical region, Sri Lanka has the upper limit value of F- concentration as 0.6 mg/l. In Sri Lanka, dental & skeletal fluorosis is a widespread health issue in majority of the residents in dry zone.

From the groundwater quality survey conducted including both CKDu endemic and non- endemic regions it is reported that high fluoride amounts is a wide spread problem in dry zone Sri Lanka, highly relating with the regions associated with CKDu prevalence. Anuradhapura, which is one of the most affected regions, has reported the highest fluoride content of 7.03 mg/l with a mean value of 1.13 mg/l. Polonnaruwa has reported a mean value of 0.84 mg/l with a maximum fluoride content of 3 mg/l, while Badulla which is another endemic region resulting with a mean fluoride content of 0.56 mg/l and a maximum value of 2 mg/l, which clearly illustrate the excessive fluoride amounts in the CKDu endemic regions. In comparison to these results, Batticaloa reports a mean fluoride level of 0.21 mg/l and a maximum fluoride level of 0.7 mg/l. However according to Jayatilake et al. (2014), Hambantota is a non-endemic area, with no reported CKDu cases. But the present study reports 0.59 mg/l mean fluoride content along with a maximum fluoride level of 2.0 mg/l. some other studies also has reported high fluoride levels in Hambantota region. Nonetheless, 61% of the samples taken from Hambantota were having a fluoride content less than 0.6 mg/l. Kandy which is a non-endemic region, has reported very low concentrations of fluoride levels with a mean content of 0.16 mg/l and a maximum value of 0.38 mg/l. Samples with fluoride content more than 0.6 mg/l (the recommended guideline value for fluoride) has exceeded in 70% and 59% of the samples tested in Anuradhapura and Polonnaruwa respectively. Other districts exceeds this limit in smaller percentages. But, being a CKDu endemic region, Badulla district which is a CKDu affected region, exceeds this upper limit in only 37% of the samples tested. But when clearly distinguish the test results, it can be clearly noticed that some specific areas in Badulla district reports very high amounts of fluoride, especially around Girandurukotte area. If considered the tested values in Girandurukotte the guideline value exceedance percentage increases up to 62%. According to Chandrajith et al, (2010) Girandurukotte is a highly endemic region of CKDu, with a 96% of the CKD patients had no relation to the conventional causes such as diabetes and hypertention.

2) Excessive Hardness

Hardness of water is occurred due to dissolved polyvalent metallic ions, and mainly due to calcium and magnesium (WHO, 2011c). Hardness in water is not considered as a health risk, but a nuisance due to its poor soap performance & mineral build up on plumbing fixtures. Water containing calcium carbonate at concentrations below 60 mg/l is generally considered as soft; 60–120 mg/l, moderately hard; 120–180 mg/l, hard; and more than 180 mg/l, very hard (WHO, 2011). According to the research results the highest hardness value 1733. 3 mg/l is reported from Hambantota district, with a mean value of 293.4 mg/l which can be categorized as very hard water. The districts which reports mean value above 180 mg/l (Very hard water) are Polonnaruwa, Anuradhapura and Hambantota, of which two of the districts categorized into CKDu endemic regions. The other three districts reports hardness values in the moderate hardness (120 – 180 mg/l) range. However, Anuradhapura is considered as the most affected district, and the reported hardness and fluoride levels are considerably high in comparison to the other districts.

3) Arsenic

Arsenic has long been known as a poison and is best known for its harmful acute effects. Long-term exposure to this poison through drinking water and/or food can results in adverse health effects including dermal diseases such as melanosis (dark and light spots on the skin) and keratosis (hardening of skin on hands and feet); vascular diseases; birth defects; low IQ; cancer of lung, kidney, skin, and others (Ngai, et al., 2005). WHO recommended guideline value is 10 µg/l (WHO, 2011a). According to this groundwater survey results, none of considered districts' mean arsenic concentrations exceeds this guideline value. Only in one location the arsenic concentrations has exceeded this guideline value, and that is from Uppodai Lake Road in Batticaloa out of all 504 well points water samples. All other reported values are almost below 3.25 µg/l. According to a groundwater survey conducted in 14 districts in 2012-2013 by Weragoda, et al. (2013b), high arsenic values are reported only in four districts, they are 15 µg/l, 66 µg/l, 13 µg/l, 14 µg/l in Puttalam, Mannar, Mullattivu and Baticcaloa respectively. But the mean value in any district has not exceeded the WHO recommended value. According to unpublished data of Weragoda et al.,(2014) it could be noticed when closely study the well point locations of higher concentrations of Arsenic levels, that they are located nearby sea or bay. Hence, there can be a direct relation with environmental factors associated with coastal area, to result

with high Arsenic levels in four different well points in coastal regions in Sri Lanka. But according to overall results a common relation with CKDu and the Arsenic concentrations, could not be recognized.

4) Cadmium & Chromium

The presence of Cadmium and Chromium in all the considered regions have found to be very lower than the recommended guideline values by WHO. The maximum Cadmium value reported is 0.22 µg/l from all regions and the guideline value is 3 µg/l. Also maximum Chromium value reported is 2.1 µg/l while the guideline value is 50 µg/l. Hence from the groundwater quality survey results of considered districts, it seems to have no relation with CKDu and high Cd or Cr levels.

5) Relation among Cations and Anions

The combination of cations and anions were investigated in 4 districts, namely Anuradhapura, Polonnaruwa, Batticaloa and Hambantota. A significant relation to CKDu prevalence and cation and anion combination could be seen only with NaFl and $MgFl_2$ presence in water. In Anuradhapura & Polonnaruwa correlation possibility of these are high, while Hambantota shows no any good correlation with fluoride ions and any cation type, which may have an effect on the case, of being an non- endemic region while having a fairly high mean value for fluoride concentration. Also Batticoloa shows a fairly good correlation among Na^{+}, Mg^{+2} and Fl^{-} ions, but the concentrations of fluoride is very lower than the recommended value by WHO. Hence from the cation and anion correlation analysis, it can be concluded that the cation anion combination of fluoride seems to have an effect on Hambantota district to be a CKDu non endemic region even with high fluoride levels reported. The proper combination of fluoride and a cation for Hambantota could not be established with the available data, hence further investigations on the presence of other heavy metals may be required.

IV. Conclusion

Etiology for the CKDu epidemiology in different countries is still unknown, while some clear relation is evident within the suggested risk factors, such as heat stress, drinking water, exposure to chemicals, heavy metals, etc. Also there are some similarities in the affected category. Main risk factor for Sri Lanka seems to be the drinking water quality. From the groundwater investigation conducted in dry zone, it was found that there's a distinct relation with the high fluoride and hardness in groundwater and the prevalence of CKDu. The cations and anion However, no any tested heavy metal (Arsenic, Cadmium & Chromium) has proven for direct correlation with the CKDu prevalence.

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Charuni Wijerathne is a BSc Civil Engineering graduate from University of Peradeniya, Sri Lanka and currently reading for PhD in Environmental Engineering.
Her research interests are drinking water quality, low cost water purification and rainwater harvesting in developing countries.