

## Aetiological factors of Chronic Kidney Disease in the North Central Province of Sri Lanka: A review of evidence to-date

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### Abstract

#### Introduction

Chronic kidney disease of unknown aetiology is a major health care problem in the North Central Province of Sri Lanka. During the last decade several researches were undertaken to identify the prevalence and aetiology of the disease. Fifteen manuscripts published in peer-reviewed scientific journals and two peer reviewed abstracts of were included in the review.

#### Results

The disease mainly affects males from poor socio-economic backgrounds who are involved in paddy farming. Mild proteinuria was present but urinary sediments were normal. Renal biopsies were reported as interstitial nephritis. Significant predictors of kidney disease in these patients included age, history of smoking, being under treatment for hypertension and drinking well water in the fields. Studies on heavy metal and ochratoxin exposure have revealed conflicting results. Fluoride content of well water in all these areas exceeded the WHO recommended level of 0.6 mg/L. Water in all areas was alkaline which could facilitate mobilization of fluoride from minerals indicating a fluoride mediated mechanism for renal damage.

#### Conclusion

The aetiology of CKDu in NCP of Sri Lanka is probably multi-factorial involving one or more environmental factors and a possible genetic predisposition in vulnerable populations.

**Key words :** Chronic kidney disease, Aetiology, Sri Lanka

### Introduction

Chronic kidney disease (CKD) has become a major public health problem worldwide. The high cost involved in the management of end stage renal failure has led to a substantial burden on global health-care resources (1). The management of CKD is even more difficult in developing countries due to lack of resources and restrictions in health care spending. The mortality and morbidity due to CKD is increasing in Sri Lanka and this burden is even more pronounced in the North Central Province (NCP) of the country where the underlying causes of CKD remain unrecognized (2).

CKD is defined as kidney damage evidenced by structural or functional abnormalities of the kidney with or without decreased GFR over a three months period. Staging of CKD into grades 1-5 according to the severity is based on the National Kidney Disease Outcomes Quality Initiative (KDOQI) criteria (3). Recognized causes of CKD worldwide include diabetes mellitus, hypertension, glomerulonephritis, obstructive uropathy and congenital diseases such as polycystic kidney disease. Prevalence of CKD in Sri Lanka is largely unknown mainly due the unavailability of renal registries and

lack of epidemiological studies. However, in-line with the global trend, there is a shift in the aetiology from infective origin to non-communicable diseases such as diabetes mellitus and hypertension (4, 5).

With the dawn of 21<sup>st</sup> century, there were reports of increasing prevalence of CKD in the NCP of Sri Lanka and soon it was recognized as a major health care problem in the province. (6). There was no association with known risk factors in majority of these patients (7) and it was debated whether this is a new disease entity. This new form of the disease is identified as chronic kidney disease of unknown aetiology (CKDu). In 2008, the World Health Organisation together with the Ministry of Healthcare and Nutrition launched the National Research Programme for CKDu. The Scientific Committee of the programme developed the criteria to define CKDu. According to this definition, CKD is considered as of unknown origin in the absence of a past history of diabetes mellitus, chronic or severe hypertension, snake bite, glomerulonephritis or urological diseases; normal HBA<sub>1</sub>C (<6.5%), blood pressure <160/100mmHg untreated or <140/90 mmHg on up to two anti hypertensive medications (8).

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The NCP where the major burden of CKDu is seen, extends over 10 530 km<sup>2</sup> in the dry zone of the country and the majority of people live in the region depend on farming for their livelihood. The disease mainly affects males from poor socio-economic backgrounds who are involved in paddy farming (2). Mild proteinuria was present (<1g/24 hours) but urinary sediments were normal. Renal biopsies of these patients were reported as interstitial nephritis indicating possible toxin exposure (9).

#### **Toxic and environmental factors in renal disease**

Various toxins and environmental factors such as heavy metals, plant toxins and high ambient temperatures (10) are potential causes for kidney damage. Several toxic mediated kidney diseases have been documented in the world medical literature. There were reports of chronic renal failure among people living in the downstream basin of the Jinzu River in Japan around 1950s. Women were mostly affected and they had bone brittleness (osteomalacia) and as a result the body movements were extremely painful hence the name "Itai-itai". The aetiology of this disease was found to be cadmium toxicity due contamination of Jinzu River from discharge by commercial activities of the Kamioka Mines. Downstream, the water was used for drinking and irrigation of paddy fields (11). Chinese herbal nephropathy is a form of interstitial nephritis first reported in Belgium in 1994. Women who have undergone slimming therapy with Chinese herbal containing aristolochic acid were affected. Aristolochic acid has nephrotoxic and carcinogenic properties and urothelial tumours were reported in some patients (12,13).

Balkan endemic nephropathy (BEN) first described in 1956 is distributed along the major tributaries of Danube River in Croatia, Bosnia, Serbia, Romania and Bulgaria. It was common among farmers and urothelial tumours were seen in most patients. Several hypotheses were suggested such as exposure to a mycotoxin (Ochratoxin A), long-term exposure to polycyclic aromatic hydrocarbons and other toxic organic compounds leaching into drinking well water from low-rank coals and chronic dietary intoxication with seeds of *Aristolochia clematitis* which grows in abundance in the corn fields. Demonstration of DNA adducts derived from aristolochic acid (AA) in renal tissues and tumour tissues of patients led to the conclusion that dietary exposure to AA is a significant risk factor for BEN and its associated transitional cell cancer (14).

An epidemic of CKD has been reported in the Pacific Coast of Central America, killing more than 24,000 people in El Salvador and Nicaragua since 2000. Most victims were manual labourers or sugarcane workers. The disease is asymptomatic in the early

stages, has a mild proteinuria possibly from interstitial origin and is not associated with conventional risk factors (15). Some believe the kidney damage is caused by toxic chemicals used in agriculture while others attribute it to long hours working in extreme heat without sufficient intake of fluids (16).

#### **Risk factors of CKDu**

During the last decade several researches were undertaken to identify the prevalence and aetiology of the CKDu in the North Central Province of Sri Lanka. Pub Med search located 15 manuscripts published in peer-reviewed scientific journals. Two peer reviewed abstracts of presentations in national scientific conferences were also included in the review. Abstracts that were not peer-reviewed and had insufficient information were excluded. Studies that were carried out before the definition of CKDu were established in 2008, absence of conventional risk factors was used as the criterion to recruit CKDu patients.

A descriptive cross-sectional study was carried out by Peiris-John et al to determine whether there was an association between chronic renal failure (CRF) and low-level organophosphate pesticide exposure (17). This study was conducted at the renal clinics of the Anuradhapura Teaching Hospital (exposed patients) and National Hospital of Sri Lanka (non-exposed patients) and Moratuwa fishing village (non-exposed controls) and Uda Walawe irrigation scheme (exposed controls). Red cell acetyl cholinesterase levels (AChE) were measured as a marker of organophosphate exposure. Red cell AChE levels among farmers exposed to pesticides were significantly lower than in unexposed controls ( $p < 0.05$ ). Among the patients with CRF, red cell AChE were lower in the exposed group as compared with the unexposed group ( $p < 0.05$ ). Although this finding does not conclude an aetiological association, long term exposure to pesticides is likely to be a predisposing factor. Since 1970s, there has been an increase in pesticide use in the region.

In a case controlled study, 183 CRF patients of unknown aetiology attending the renal clinic at Teaching Hospital Anuradhapura were compared with a control group from the general medical clinic of the same hospital (18). Several risk factors were evaluated. Being a farmer ( $p < 0.001$ ), using pesticides ( $< 0.001$ ), drinking well water at home ( $p < 0.001$ ) and in the field ( $p = 0.036$ ), having a family member with renal dysfunction ( $p = 0.001$ ), having taken ayurvedic treatment in the past ( $p < 0.001$ ) and a past history of snakebite ( $p < 0.001$ ) were risk factors of CRF of unknown aetiology. In the multivariate logistic regression analysis, significant predictors of CRF of unknown aetiology included having a family

member with a history of chronic renal dysfunction, a history of having taken ayurvedic treatment and having had a snake bite in the past. Subjects with a family member with renal dysfunction were 4.5 times more likely to have CRF of unknown aetiology compared with those without such a family history. Family history of renal dysfunction suggests a genetic aetiology of the disease but could also be due to the same environmental exposure such as drinking same water or consuming same food items. The use of pesticides was excluded in the multivariate model. Hence it is unlikely that long-term low-level exposure to pesticides has an impact on the development of CRF. Snakebite can give rise to CKD but given the high incidence of snakebites in some other parts of the country also, the high prevalence of CRF in the NCP cannot be explained by this. *Aristolochia indica*, a creeper plant found in Sri Lanka and India, has been used as herbal medicine in the past. It does not grow in abundance in NCP and any contamination of paddy cultivations is unlikely.

Estimation of microalbuminuria (MA) is recommended as a screening test to detect patients at an early stage of CKD. Microalbuminuria is defined as urinary albumin excretion between 20-200 mg/g in men and 30-300 mg/g in women, using the urinary albumin-to-creatinine ratio in a random urine sample; 30-300 mg/24 h, if measured in a 24h urine collection. In a community based study, risk factors for microalbuminuria were evaluated in 425 females and 461 males from Medawachchiya, Padaviya and Rajanganaya (19). The prevalence of MA was 6.3% in females and 8.6% in males. In the binary logistic regression analysis, the significant predictors of microalbuminuria included age, history of smoking, being under treatment for hypertension and drinking well water in the fields. Subjects with a history of smoking and subjects under treatment for hypertension were 3.5 times more likely to have microalbuminuria as compared to those who had no history of smoking and those who did not undergo treatment for hypertension. Subjects who drank well water in the field were approximately two-and-a-half times more likely to have microalbuminuria as compared to those who did not do so. Majority (93%) used water from the well situated in the home garden as the drinking water source at home but 33.2% of females and 45.7% of males were drinking water from the well situated in the field while they were at work.

Athuraliya et al reported prevalence, demographic characteristics and risk factors for proteinuric-CKD in three areas in the Central (Yatinuwara), Southern (Hambantota) and North Central (Medawachchiya) Provinces (9). The prevalence of CKD in Medawachchiya was reported as 5.1% ( 95% CI

4.2–5.9, n = 2600) compared to 2.3% in Hambantota ( 95% CI 1.8–2.9, n = 2844) and 9.5% in Yatinuwara ( 95% CI 7.5–12.0, n = 709). Conventional risk factors of CKD such as diabetes and hypertension were not seen in the majority of patients from Medawachchiya. The percentage of patients with CKDu was higher in (109/130, 84% ) Medawachchiya compared to Yatinuwara (2/68 2.9%) and Hambantota (6/66, 9.1%). A high proportion of CKDu patients in Medawachchiya were young farmers, had mild proteinuria without active sediment, had bilateral small echogenic kidneys and renal biopsies showed tubulointerstitial disease. On the basis of this clinical profile, the authors proposed a possible toxic aetiology making farmers in a specific geographical area been more vulnerable to the disease.

### **Fungal and bacterial toxins**

Above observations led to further studies investigating for possible aetiological factors mainly nephrotoxins in food items and drinking water sources in endemic areas. Ochratoxin A (OA) is a naturally occurring fungal toxin with carcinogenic and nephrotoxic properties. It is produced mainly by *Penicillium* species in cold climates; by *Aspergillus* species in tropical climates and is present as a contaminant in many food items (20). The widespread occurrence of OA in food and animal feed could lead to possible human exposure. OA levels were tested in 98 food samples, comprising two principal types of cereals predominantly cultivated and consumed by people in the NCP (21). Samples were collected from retail outlets in Medawachchiya, Padaviya and Rajanganaya. The results indicate that OA was a natural contaminant of cereals and pulses cultivated in these areas, but the levels detected were below the statutory maximal limit. However further studies by Desalegn et al demonstrated higher rates of urinary ochratoxins in CKDu patients in the NCP and unaffected relatives as compared to Japanese controls suggesting exposure to be common in the region (22).

Cyanobacteria also known as blue-green algae are a phylum of bacteria that grow in calm nutrient-rich water. They often grow in extensive colonies that are visible and some species produce toxins that affect humans and animals. People are mainly exposed to cyanobacterial toxins by drinking or bathing in contaminated water. These toxins can cause skin, hepatic and neurotoxicity in humans and nephrotoxicity in animals (23). Dissanayake et al studied the short term effects of extracts of cyanobacteria isolated from two reservoirs in Ulhitiya and Padaviya. They observed acute tubular necrosis in mice fed with these extracts for one week (24). These observations focused on cyanobacterium toxins as another potential nephrotoxin present in



this environment. However, ingestion of toxins through contaminated water is unlikely as majority of people in the area use ground water for drinking and cooking.

### **Fluoride and heavy metals**

Fluoride is widely distributed in the environment but is not well known as a nephrotoxin. There are few studies on fluoride induced renal damage and animal studies have shown various histological changes in the kidney (25, 26). Illeperuma et al put forward the hypothesis that fluoride could be the causative factor for CKDu and aluminium playing an additive effect by enhancing the absorption of fluoride (27). This was based on the observation that areas affected by CKDu are situated in the fluoride belt of the country and people in these areas were using substandard aluminium pots for cooking and storing of water. They observed that under acidic conditions e.g. use of tamarind for cooking, leaching of aluminium from the pots was even higher. The dissolved aluminium forms complexes with fluoride and these complexes have the ability to pass through the cell membranes. These complexes release fluoride ions inside kidney cells causing toxicity. However, there are other areas in the country with high levels of fluoride in the drinking water such as Ampara, Monaragala and Wellawaya where similar utensils are used by people but chronic kidney disease is not prevalent among them. Further, features of fluorosis and aluminium toxicity are not seen in CKDu patients and detailed studies are needed to ascertain this hypothesis.

Further studies are available on the contaminants and quality of drinking water in the region. Drinking water in the rural areas is obtained mainly from wells while reservoirs are the main source of irrigation for paddy lands in the NCP of Sri Lanka. Bandara et al have found high levels of cadmium (Cd), iron (Fe) and lead (Pb) in five reservoirs in the high CKDu prevalent areas (28). Dissolved Cd in reservoir water and sediment was 0.03 to 0.06 mg/L and 1.78 mg/L, respectively. This is much higher than the Maximum Contaminant Level Goal of 0.005 mg/L or 5 ppb recommended by the US Environment Protection Agency. Cd content in lotus rhizomes and fish was reported as high. The Provisional Tolerable Weekly intake of Cd, based on the extreme exposure by rice and fish, was also found to be high in the region (29). They attributed the high cadmium levels to the heavy use of Cd contaminated fertilizer in the region. These observations have led to the hypothesis that cadmium, a well known nephrotoxin could be a likely aetiological agent of the CKDu. However, these findings were later challenged by Chandrajith et al (30). They collected drinking water and rice samples from endemic and non-endemic regions, and urine samples from patients,

asymptomatic relatives and healthy control urine samples from a non-endemic region. Samples were analyzed for trace and ultra trace elements including heavy metals Cd and uranium (U) using ICP-MS. The fluoride content in water samples was measured using the SPADNS method. The results indicated that drinking water from both endemic and non-endemic regions contained moderate to high levels of fluoride. The Cd content in drinking water and rice from endemic regions and urine from patients and healthy people was much lower indicating that Cd is unlikely to be a contributing factor for CKDu in Sri Lanka. Other trace metals including U levels were also lower compared to the WHO recommended levels indicating that the well water in these areas is not contaminated by heavy metals. They also analyzed the surface water from the same reservoirs and rice grains from the same study area but the Cd levels were not shown to be elevated as reported by Bandara et al (29). Furthermore, according to them features of Cd toxicity were not evident among the CKDu patients.

Chandrajith et al further studied the geo-chemical properties of water. Well water samples were randomly collected from CKDu endemic regions of Giradurukotte, Nikawewa, Medawachchiya and Padaviya while Huruluwewa and Wellawaya were included from non-endemic regions (31). Huruluwewa is a village in the North Central Province which has a very low prevalence of CKDu (24). Electrical conductivity (EC), alkalinity and fluoride levels were measured. The mean content of fluoride in endemic CKDu areas of Girandurukotte, Nikawewa, Medawachchiya and Padawiyaya was 0.66, 1.21, 1.03 and 0.62 (in mg/L) respectively. In non endemic areas of Huruluwewa and Wellawaya mean fluoride content was 1.42 and 1.05 respectively. Fluoride content of well water in all these areas exceeded the WHO recommended level of 0.6 mg/L. Water in all areas was alkaline which could facilitate mobilization of fluoride from minerals. There was a large variation in the Na/Ca ratio between endemic and non-endemic areas. It was noted that Ca-bicarbonate type water is predominant in endemic CKDu regions whereas Na-K-non dominant anion type water is common in the non-endemic regions. They concluded that the cytotoxicity properties of fluoride appear to be due to the effect of  $\text{Ca}^{2+}$  and  $\text{Na}^+$  of the ingested water on the fluoride metabolism. This study illustrates another possible fluoride mediated mechanism for renal damage in people living in endemic areas.

### **Conclusions**

The aetiology of CKDu in NCP of Sri Lanka is probably multi-factorial involving one or more environmental factors and a possible genetic predisposition in vulnerable populations. Although

no single environmental factor or toxin identified so far, it is likely that drinking water is associated with the occurrence of the disease. Early detection is possible by screening for proteinuria and control of blood pressure with angiotensin converting enzyme inhibitor (ACEI) therapy may be helpful in delaying the progression to end stage renal failure (33). Until the aetiology is established, provision of safe drinking water to the affected communities seems to be the only feasible option in disease prevention.

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