

Chronic kidney disease (CKD) is emerging as an important chronic disease globally. This is equally true about India with its huge population more than 1.25 billion, CKD is going to be an important non communicable disease in future. It has been recently estimated that age adjusted incidence rate of ESRD in India will be 229 per million populations¹ and more than 1 lack new CKD patients need renal replacement therapy annually in India.²

Although diabetes and hypertension are the important causes of CKD, a large number of patients develop CKD due to unknown etiology. This form of CKD recently labeled as CKD of unknown etiology (CKDu) is found frequently and studied extensively in Sri Lanka, El Salvador, Guatemala, Nicaragua, Bulgaria, Croatia and Serbia. In India more studies are required to find out the extent and etiology of this new entity.

The endemic nature of chronic kidney disease of unknown etiology (CKDu) was first observed in 1999 and over the past 15 years the prevalence of the disease within certain geographical locations has increased dramatically. This disease is characterized by its disassociation with the well-known risk factors such as diabetes, hypertension or chronic glomerulonephritis. The disease remains asymptomatic, and usually presents as end stage kidney disease.³

Couser et al⁴ in his review of CKD in developing countries mentioned that the percentage of CKDu is considerably higher in developing countries than developed ones. International Society of Nephrology –sponsored screening program in China, Mongolia and Nepal revealed that 43% of people with CKD did not have diabetes or hypertension.⁵

ISN has released a position statement on the epidemics of chronic kidney disease stating that CKDu has become a worldwide concern⁶. These epidemics typically affect poor agricultural communities, adults of working age affecting individual's social and economic aspect of, frequently leading to death even when renal replacement therapy is available. CKDu imposes a formidable challenge to local health systems due to high-cost. There is a need to understand the cause of the problem, so that appropriate preventative measures can be implemented⁶.

DEFINITION

Various authors have defined CKDu differently. While there is no internationally accepted case definition, common characteristics across studies include the following:

1. Asymptomatic and progressive CKD
2. Absent or sub-nephrotic proteinuria
3. Absence of hematuria
4. Absence of diabetes, chronic or severe arterial hypertension, HIV, snake bite, glomerulonephritis or other urinary tract disease
5. Normal glycosylated hemoglobin (<6.5%)
6. Blood pressure
<160/100 mmHg in untreated patients
<140/90 mm Hg in patients receiving up to 2 antihypertensive drugs⁷

PATHOLOGY

The main pathology is seen in proximal tubules and interstitium. Clinically the disease is characterized by tubular proteinuria usually β_2 – microglobulinuria and the absence of hypertension and edema. The histological appearance of the disease reveals tubulointerstitial pathology that is similar to toxic nephropathies⁸. To date, there is no unequivocal evidence to a recognizable possible environmental causative factor responsible for the CKDu.⁹

CKDU IN SHRILANKA

A retrospective, descriptive hospital cohort study carried out during the period 2001-2002 in clinics in Anuradhapura and Kandy found that the majority of patients seeking renal care were CKDu patients.⁸ Recent investigation from community based study in Sri Lanka report significantly higher rate (12.9 %). The most number of CKDu patients have been reported from three provinces that in NCP, UP, EP in Sri Lanka.²

CKDu in Sri Lanka is more prevalent among men (ratio of 3:1), around the age of 40 to 60 years and who are engaged in agriculture. The suspected causes are episodic dehydration, smoking and consumption of illicit liquor.¹⁰ The causal factors that have been suggested that may contribute to the development of the disease include heavy metals like cadmium, arsenic various nucleotides, including uranium, elevated levels of fluoride in ground water, the specific composition of groundwater, aluminum and Aflatoxin. Although there is not sufficient evidence to state that cadmium is likely to play a significant role in the development of the disease, high levels of fluorides present in their ground water may interact with other constituents that are present namely

Table 1: Attack rates per 1000 workers by occupation at a large sugar estate in Chichigalpa, Nicaragua, 2010–2014¹⁶

Occupation	Attack rate per 1000 workers
Shrimp farm worker	109.1
Irrigation and drainage worker	61.8
Cane collector/harvester	35.7
Cane cutter	35.5
Weed control worker	34.0
All other occupations	11.7

calcium, sodium and possibly magnesium. This has still to be confirmed. Although it is suggested that aluminum vessels may have a role to play in the development in the disease but there is no supporting evidence. This is also true about Aflatoxin contamination as a significant causal factor responsible for development of the disease in Shri Lanka. Role of genetic link may be responsible as the disease appears to be familial.³

The number of CKDu was likely to reach over 2000 by the end of 2013¹¹. These patients are concentrated in the dry regions of the country affecting both men and women, between the ages of 30 and 60 years. The majority of patients are poor farm workers. Multiple factors may be linked in combination like environmental factors, diet practices and genetics¹¹.

The research conducted in Shri Lanka by Ministry of Health (MOH) and WHO, tested blood, urine, hair, and nail from both CKDu patients and controls. They tested a number of environmental samples including water, rice, fish, tobacco, and selected root crops. Exposure to sun, heat, stress and dehydration were thought to be potential contributing factors to CKDu and populations at lower elevation may be at lower risk. These patients work in hot dry zones and spent hours in the fields with limited water intake and are not over weight and hypertensive².

Exposures from pesticide or fertilizer which contain cadmium can enter the environment through repeated agricultural applications. This is also true about phosphate fertilizers which contain traces of cadmium and heavy metals. The pesticides may also be a cause of concern. The high level of minerals may also be seen in hard water that is fluoride or heavy metals like cadmium, uranium and lead in ground water wells. However, the environmental risk factors do not consistently show elevated throughout the endemic area.^{8, 12}

The MOH/WHO in Shri Lanka estimates that 15 % or more of the population in certain endemic area are at risk of developing CKDu. There are certain things which are not clear from this study.

- Although previous studies showed that men were more prone to CKDu this study showed more women affected by CKDu.
- The results of this study indicate that cadmium

exposure is a risk factor for CKDu which is not seen in previous studies.

- Cadmium was below the permissible limit in rice. Although cadmium was high levels in tobacco and lotus roots it was found that people rarely get to consume these seasonable vegetables.
- The water sources had cadmium, lead and uranium in permissible limits which does not explain the source of element in the food chain
- Although the cadmium was found in the urine of these patients drinking water cadmium was within normal limits.

To resolve these discrepancies more research is necessary.¹³

MESOAMERICAN NEPHROPATHY

Central America has recently gained international attention due to an outbreak of unexplained and severe kidney disease. This is labeled as “Mesoamerican Nephropathy.” This is mostly found in young male sugarcane workers in Central America and was reported in late 1990.¹⁴

Pan American health organization and WHO (PAHO/WHO) highlighted the urgent need for research to discover the cause of this nephropathy. The highest kidney related mortality in the world is reported by O Ramirez¹⁴ in Nicaragua and L. Salvador. L.K. O’Donnell¹⁵ found that in Nicaragua the disease affects primarily young men from poor, rural areas who are mainly agricultural workers.

In the sugar estate the role of *Leptospira* has been suspected in the transmission of disease. Run-off water from the fields, to which workers were exposed, is likely contaminated with urine from rodents.

As shown in table 1 the attack rate is more seen in workers in irrigation and drainage, as well as shrimp farmers at the sugar estate compare to other occupations like Cane cutters. These workers come in contact with contaminated water through breaks in the skin contact with mucous membranes, or by ingestion.¹⁶

Although identified since 2 decades the etiology of Mesoamerican Nephropathy remains unknown.

CKD U IN INDIA

Agarwal SK¹⁷ reported that the epidemiology of CKD in India is different from that in European and western world. Indian patients are younger and present with small kidneys and do not have known etiology of CKD. He concludes that a nationwide reporting system or registry is a necessary to determine the true incidence and prevalence.

Indian Society of Nephrology published the Indian CKD registry¹⁸. The data collected from 2005 showed that 16 % of the adult CKD patient had CKDu. These patients belong to low income group. CKDu was found to be the second biggest cause next to diabetes.

The study published in Lancet July 2013 shows that India contributes to about 20% of CKDu cases worldwide.¹³

Ajay K. Sing et al.¹⁹ studied the epidemiology and risk factors of Chronic Kidney Disease in India. The results were published as SEEK study (Screening and Early Evaluation of Kidney Disease). This study included patients from urban area with high school diploma and from higher income group who were mostly over weight. The risk factors were hypertension 64.5 %, diabetes 31.6%. As this study was from urban area did not get cases of CKD of unknown origin due to selection bias. Hargovindsing Trivedi²⁰ from IKDRC Ahmedabad found diabetes in 9.79 %, hypertension 26.87%, obesity 18%, over weight 32.85%, stone disease 17.19%. Urine albumin was present 13.79 % of patients. As this study was from semi urban population there were no patients of CKDu.

The study carried out in Odisha by Social Human Action for Rural Poor (SHARP) which included villages including Rautabhuin found 100 new cases of CKDu. ICMR and RMRC in Bhubaneswar carried out a survey in Nursingpur. It was found that 8-12% people suffer from CKDu. Such findings are also observed in Cuttack, Bhubaneswar, Jaipur, Balangir, Kalahandi, Jharsuguda and Koroput. ICMR has now identified Odisha as 1 of the two CKD hot spots the other being Andhrapradesh.¹³

Preliminary data from the research carried out form Andhra Medical College, Tatapudi and Harward Medical School found high levels of silica in water samples from Shrikaculam. Although Gangadhar found high levels of strontium and silica in water samples from Prakasam. He suggests that only silica may be responsible for the disease. WHO India and National Geophysical Research Institute (NGRI), however ruled out silica as the cause of problems in Shrikakulam in Parkas. D.V Reddy of NGRI and A.Gunasekar of WHO India found that ground water in Shrikakulam is less mineralized than that in Prakasam. Concentration of inorganic chemicals were within permissible limits for drinking water. State of Andhrapradesh including costal Uddanam and inland of Chimakurthy Mandal reported CKDu in younger males from rural costal area from low socio economic group. They are involved in cultivation of coconuts, rice, Jackfruit and cashews.¹³

CKD U IN MAHARASHTRA

We carried out hospital based pilot (unpublished) study at Marathwada region of Maharashtra including 560 patients of CKD over 2 years period between 2014 and 2015. We found 40% of patients had CKDu while diabetes and hypertension were present in 14% and 28% respectively. Males predominated, male to female ration being 5:2. 52% of patients belonged to age group of 21- 40 years, active age group. 95% of patients had BMI <24.5 Kg/per square meter and 60% patients had proteinuria. Majority patients presented in stage IV and V with shrunken kidneys. 90% of patients were agricultural farm workers or laborers. 45% of patients were illiterate. 39% used tobacco and 15% consumed alcohol. NSAIDs use was seen in 25% and smoking and alcohol both were present in 17% of patients.

The type of water consumed was from either well water or ground water.

A key note address by Dr. Shanthi Mandis in 2013 summarizes the present state of research in CKDu.²¹ The prevalence of CKDu is 12.9% to 16.9% in various studies. A male to female ratio is variable. There is no definite etiology for CKDu. The suspected factors in the etiology in CKDu are low levels of cadmium exposure through the food chain, exposures to heavy metals and selenium deficiency. The genetic susceptibility is likely cause of CKDu as the disease is seen in families. The use of Sapsand in Herbal Medicine may be responsible for CKDu. Fluoride and calcium in water may aggravate cadmium toxicity. Enalapril can be used to reduced albuminuria in CKDu.

WHO RECOMMENDATIONS²¹

1. Supply clean drinking water (pipe borne) to mitigate contributing factors that may aggravate the effect of nephrotoxins including high calcium, fluoride and heat /dehydration related harmful effects on kidney.
2. Explore the use of rock phosphate and regulate Cd, As, Pb in phosphate fertilizers and indiscriminate use of synthetic fertilizers.
3. Strengthen tobacco regulations to further protect people including children from exposure to Cd through passive smoking.
4. Advice people to avoid use of lotus roots from the endemic area (avoid exceeding PTWI)
5. Further research e.g. explore methods to reduce the intake of Cd by plants by maintaining soil at neutral pH and other affordable measures.
6. Ensure appropriate disposal of Nickel Cadmium batteries , plastics, bottle lids .
7. Diazinon, Propanil, Paraquat, Chlotpyriphos, Carbaryl-monitor the ban in the NCP. Regulate the use of pesticides.
8. Create the awareness (public/doctors) of the danger of inappropriate use of nonsteroid analgesics.
10. Provide facilities for early diagnosis and ACEI for treatment.
11. Health education to safeguard the health of the general population including farmers.
12. Provide social welfare support to affected families.

Joint efforts by clinicians, scientist, health organizations and politicians are required to control the epidemic of CKDu in developing countries. This will reduce the financial burden of treating end stage renal disease in poor population mainly affected by CKDu.

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