

## Observational Study

# Chronic kidney disease of unknown etiology : an emerging health care burden

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Chronic kidney disease of unknown etiology is an emerging health care burden in certain geographical areas in south Asia which affects a large population of young and middle aged adults. Regions in India such as Uddanam, of Srikakulam district and Prakasham district of Andhra Pradesh, Goa, Odisha and North central province of Sri Lanka have the largest population of affected individual who predominately belong to the farming community. The etiology is unknown with tubulointerstitial involvement which is progressive. Screening, surveillance and supportive management are discussed.

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**Key words :** Chronic kidney disease of unknown etiology, farming community.

Chronic Kidney disease of unknown (CKDu) etiology remains an enigma. It is a serious public health problem in developing countries of Central and Latin America, South Asia predominantly affecting people belonging to the farming community. The large majority of the people affected are farm workers, earning menial income. The international community including nephrologists, epidemiologist, and other researchers are exploring the role of potential risk factors for the development of CKDu. In the South Asian region the first reports of this epidemic in North Central province of Sri Lanka was brought to light by the efforts of Prof. Tilak Abeysekera<sup>1</sup>. Following this many other reports were published by scientists and researchers from Sri Lanka. Of the 21 million population, nearly 1.7 million people live in the affected areas and 69,258 patients are currently attending clinics (CKD G1–G5). Studies show the following distribution: CKD G3 (31.8%), CKD G4 (40.0%) and CKD G5 (24.5%)<sup>2</sup>. The President of Sri Lanka His Excellency Maithripala Siresena set up a presidential task force to urgently do consultation and guide future direction for addressing CKDu in Sri Lanka. The WHO set up a task force with expert consultation to design a step wise approach to understand the burden, geographical distribution and time trends of CKDu in Sri Lanka which would also serve as a platform for longitudinal follow up studies to explore role of potential risk factors (Fig 1). The first and second author of this article have been involved in the CKDu conceptual framework

to implement the recommendation by the National science foundation, WHO and Gardiner ISN fund for studying the CKDu in Sri Lanka.

The burden of CKDu as an emerging problem in certain geographical areas of India was brought to the notice of the State health authority and the Central government by Prof. Ravi Raju, and Prof Gangadhar Thaduri and Prof Ajay Singh<sup>3,4</sup>. This was

predominantly noticed in the Uddanam of Srikakulam district and Prakasham district of Andhra Pradesh, Goa, Odisha (Fig 2). The Andhra Pradesh Government and the Indian council of Medical research are collaborating with other stake holders to find out the geographical distribution, time trends for a longitudinal follow up of the individuals in the affected regions. A CKDu core committee met under the leadership of Prof Ravi Raju comprising pathologists, geneticists, epidemiologists, nephrologists (Indian society of nephrology) sponsored by TANKER foundation Chennai and Madras medical mission, Hospital in July this year to form a conceptual framework for defining case definition, protocol for periodic community base surveillance and improved data collection and flow.

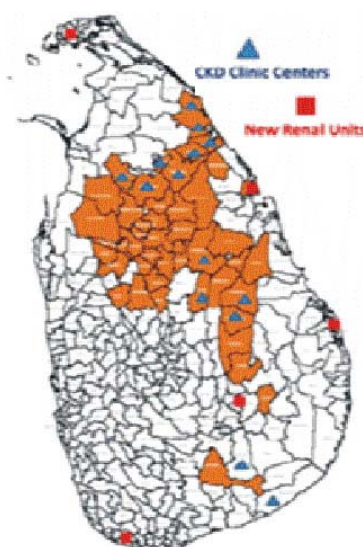


Fig 1 — CKD/CKDu prevalence in Sri Lanka

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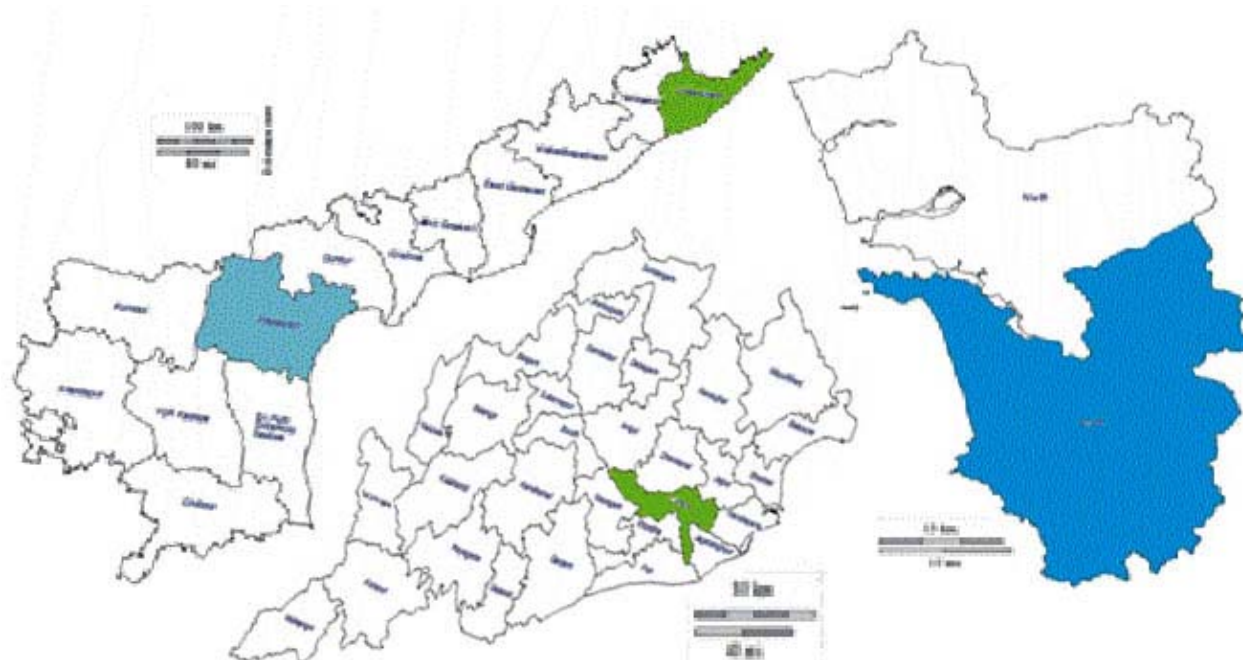


Fig 2 — Clockwise top left Odisha, Goa and Andhra Pradesh

This core group meeting was supported by nephrologists from Sri Lanka, WHO representative from Sri Lanka and ICMR (Fig 3).

**Operative Definition of CKDu :**

- (1) Geographical residence in the affected areas
- (2) No evidence of preexisting Diabetes Mellitus or Hypertension
- (3) Minimal protienuria
- (4) Renal biopsy showing tubule interstitial disease.

**Etiology of CKDu :**

It predominantly affects the farming population of the

Uddanam region that lies in north-coastal Andhra consisting of the mandals of Kaviti, Sompeta, Kanchili, Ithapuram, Palasa and Vajrapukotturu, accounting for more than 100 villages in total. Various causative associations such as occupation, environmental toxins such as high content of phenol, mercury and silica in drinking water have been also been thought to be involved in the pathogenesis of CKDu. However none of the above postulates have been proved scientifically. Heat stress is not an issue in the Uddanam area. The role of genetic factors is yet to be determined. In surveillance program at Srikakulam over hundred thousand people were screened for CKDu and 13% of the population was found to have serum creatinine of =1.2mg/dL. The other geographically CKDu involved areas require further studies to look at the prevalence of CKD.

**Investigations :**

This requires a team effort to develop a protocol for the periodic community based surveillance. There should be a plan, improved data linkages and flow. Basic investigations should include a questionnaire to be collected from each household in the affected areas (Table 1) which should contain family history, medication intake (including alternative medication and analgesics), body mass index, blood pressure recording, serum creatinine, fasting blood sugar estimation, routine urine analysis and special strips for microalbuminuria estimation. Stratification of patients according to stages of CKD is mandatory (either use Cockcroft and Gault formula/ CKD-EPI formula). Further to this, genetic study of kidney biopsy specimens would be useful to look for particular genotypes, metabolomics

Table 1 — Conceptual framework for establishing a community – based surveillance and longitudinal cohorts :  
A step-wise approach to CKDu

Step 1 : Establish community based surveillance		
Define the geographical area and ensure high participation	Collect contextual environmental and socioeconomic data on the population	Core questionnaire eGFR, dipstick, blood pressure, etc
↓		
Step 2 : Focus on exposure / Interventions of interest		
Add specific protocols in defined populations with exposures of interest, e.g heat exposures, specific chemicals, sources of drinking		
↓		
Step 3 : Longitudinal follow up studies		
Cohorts can be established in select populations based on results from step 1 and 2 and other emerging knowledge		

and proteomics of the serum and stool samples in the CKDu population to compare with healthy cohort.

### *Management Strategies :*

Conservative management include avoidance of nephrotoxic agents, diet and purified drinking water to eliminate exposure to silica, phenol and mercury. It was found that drinking water from bore wells in the Uddanam area after reverse osmosis treatment 80% is reject, highlighting the importance of clean drinking water. Exposure to agrochemicals for farming is a subject of debate, hence caution should be exercised in their use. Patients in CKD G5 requires renal replacement therapy. The Sompeta community health center which can be easily accessed by the affected people in Uddanam can be upgraded to provide hemodialysis facilities training for home peritoneal dialysis (CAPD) and as a research center. Other supportive treatment for CKD such as anemia correction, CKD MBD, skilled dietician service and regular follow up through primary health center with increased man power should be provided to cope with ever increasing population of CKDu patients.

As most of the uremic toxins originate in the gastro intestinal tract, there is increasing evidence to show the benefit of ingesting prebiotics and probiotics for slowing down the progression of CKD. These preparations contain combination of bacilli (*Streptococcus thermophilus*, *Lactobacillus acidophilus*, *Bifidobacterium longum*) with indigestible fiber which may modify the microbiome of the gastro intestinal tract and hence reduce the generation of uremic toxins and improvement of eGFR in the early stages of CKD. This may be a cheaper alternative for the management of CKDu patients who belong to the lower socio economic status, who cannot afford renal replacement therapy. The selection of prebiotics, probiotics should be based on the authenticity of the particular product which has undergone research and validation<sup>5,6</sup>.

### *Monitoring Kidney Functions in CKDu :*

Minimum frequency for repeating renal function tests (for proteinuria and creatinine.) Also check serum electrolyte if available

Stage G1	eGFR >90, Annually
Stage G2	eGFR 60-89, Annually
Stage G3	(known to be stable) eGFR 30- 59, Annually
Stage G3	(newly diagnosed or progressive) eGFR30-59, 6 monthly
Stage G4	(known to be stable) eGFR 15-29, 6 monthly



Fig 3 — CKDu core group members

Stage G4 (newly diagnosed or progressive)  
eGFR 15-29, Quarterly

Stage G5 eGFR<15, Quarterly,

(1) a: stable kidney function defined as change of eGFR<5 ml/min/1.73 m<sup>2</sup> over one year or more

(2) b: progressive kidney damage defined as change of eGFR >5 ml/min/1.73m<sup>2</sup> over one year or less

Kidney function should also be checked during inter-current illness and perioperatively in all patients with G2-G5 CKD.

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