Distribution and Determinants of Chronic Kidney Disease of Unknown Etiology: A Brief Overview

Abstract

Globally, 33187000 DALYs and 956000 deaths are attributed to chronic kidney disease (CKD) every year. Diabetes and hypertension are the two most common causes of CKD. Another category of CKD without any known common causes, chronic kidney disease of unknown etiology (CKDu) is also increasingly reported from different regions of the world such as Central America, Sri Lanka, and India. They are predominately observed in agricultural communities where crops such as sugarcane and coconut are commonly cultivated. Young adults and males are at higher risk of developing CKDu. It mainly affects individuals belonging to lower socioeconomic status. Exposure to silica, arsenic, and fluoride might be associated with increased prevalence of CKDu. The role of heat stress in contributing to CKD through dehydration is unclear but cannot be ruled out. Mycotoxins such as aflatoxins and ochratoxins are also found to be associated with CKDu in some settings. Several studies have reported that CKDu has a significant positive association with pesticides used in agriculture such as HCH, Endosulfan, Alachlor, and Pendimethalin. There is also a possible role of infections by Hantavirus and Leptospirosis in acute febrile phase of CKDu. However, there is no conclusive evidence from studies conducted on CKDu regarding its causes and risk factors. Therefore, large-scale studies with better methodology need to be conducted to study the etiology and pathogenesis of CKDu in various settings.

Keywords: *Chronic kidney disease of unknown etiology, chronic kidney disease, risk factors, unknown etiology*

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Introduction

Globally, chronic kidney disease (CKD) is one of the leading causes of disability and deaths among all non-communicable diseases (NCDs) contributing to 33187000 disability adjusted life years (DALYs) and 956000 deaths in 2013.[1,2] CKD is defined as reduced glomerular filtration rate (GFR <60 ml/min) and/or kidney damage (structural or functional abnormalities other than GFR) for more than 3 months.[3] Common causes and risk factors of CKD are ageing, genetic predisposition, smoking, alcohol intake, obesity, diabetes, and hypertension.[4] Without the presence of these risk factors, CKDs have been reported from different parts of the world including Central America, Sri Lanka, and India.[5-7] According to KDIGO 2012 Clinical Practice Guidelines, they are known as chronic kidney disease of unknown etiology (CKDu).[8] They are also known as chronic agricultural nephropathy (CAN) and CKD of multifactorial origin (CKD-mfo).[9,10] There are several explanations that CKDu could be due to exposure to specific diet, environmental toxins, heat stress, infections, and others. In this review, we summarized the distribution and possible determinants of CKDu throughout the world [Table 1].

Distribution

In agricultural communities of El Salvador, the prevalence of CKDu was found to be 15.4% to 21.1%.[11] In another Mesoamerican country Nicaragua, it was 12.7% based on reduced glomerular filtration rate (GFR) alone.[12] These are predominately agricultural communities where the main crop of cultivation is sugarcane. Prevalence was found to be lesser in communities, which cultivate coffee more compared to sugarcane (6.5%). Urinary renal damage markers were used for measuring the prevalence in the above study.[13] In Sri Lanka, the prevalence was ranging from 2.3% to 9.5%, especially in the provinces of North Central, Eastern,

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Table 1: Potential risk factors for chronic kidney disease of unknown etiology

Distribution	Determinants
Adults	Heavy metals
Males >females	Arsenic
Lower socioeconomic status	Cadmium
Inadequate health care delivery system	Lead
	Heat stress and dehydration
Agricultural communities	Mycotoxins
Sugarcane	Aflatoxins
Chena	Ochratoxins
Coconut	Fumonisins
Cashews	Agrochemicals
	Infections
	Hantavirus
	Leptospira

and Uva.[14] There are also predominately agricultural areas where chena cultivation is popular. Chena cultivation is a primitive form of cultivation where a farmer cuts down the trees of a small area of land in the jungle, sets fire to the woody growths, and cultivates the land, moving on the next year to fresh land.[15] The prevalence was found to be very high (61%) in the Udhanam district of Andhra Pradesh, India based on reduced GFR. In this district, the predominant crops cultivated are coconut, cashews, rice, and jack fruit. Variations in the prevalence of CKDu could be explained by the variations in their geography, cultivation, and different definitions of CKDu.[16] Mostly adults working in agriculture for a longer duration were affected in all the communities. However, low prevalence of CKDu in older age groups suggests that pathology occurred due to recent exposure.[15,17] In almost all sites of CKDu reported, males were affected more than females.[11-13,16,18] However, it was slightly higher in females than males in few communities of El Savlador.[19] Almost all the affected individuals belong to lower socioeconomic status.[20] Most of the affected hotspots are located in countries with poor health care delivery system where there is also lack of information regarding the actual burden of chronic diseases including CKDu. Therefore, the incidence of CKDu may be much more than what is being reported. This also contributes to increased incidence of end-stage renal disease among them.

Determinants

Heavy metals

Based on the distribution of CKDu with respect to sociodemography, occupation, and geographical factors, it is hypothesized that the disease could be related to the environment. Role of heavy metals such as cadmium, arsenic, lead, and others present in water, food, and fish have been studied. Chandrajith *et al*. found that sodium and calcium interactions in the presence of fluoride could be associated with the increasing prevalence of CKDu in Sri Lanka.[21] In Andhra Pradesh, India, researchers found that CKDu may be associated with high levels of silica in drinking water sources.[22] Studies conducted in Sri Lanka and Central America found that lead levels were not elevated in CKDu patients.[15,23] In a systematic review by Zheng *et al*., it was found that elevated levels of arsenic in the communities were associated with CKD.[24] It was further confirmed by reduction in renal disease mortality following the cessation of exposure to arsenic.[25] Similarly, studies conducted by Rango *et al*. and Nanayakkara *et al*. found that there were no clear relationship between the presence of heavy metals in drinking water and CKDu.[26,27]

Heat stress

In hot working environment, dehydration due to heat stress can affect the renal function of the employees. Similarly, recurrent volume depletion could lead to cumulative subclinical damage of the kidney resulting in CKD. In a large nationwide cohort study conducted among 37816 workers, it was found that the odds of developing kidney disease among men exposed to prolonged heat stress was 2.22 times that of men without such exposure (95% CI, 1.48–3.35). One of the limitations of this study was that both the exposure and outcomes were self-reported.[28] However, a study by VanDervort *et al*. found that there was no clear association between ambient temperature and CKDu.[29]

Mycotoxins

Desalegn *et al*. conducted a study among CKDu patients of North Central Province of Sri Lanka to identify the presence of nephrotoxic mycotoxins in their urine samples. They found that 61.29%, 93.5%, and 19.4% of the CKDu patients had aflatoxins, ochratoxins, and fumonisins in their samples, respectively. They also compared the levels with their healthy relatives and healthy Japanese individuals. Patient's mycotoxins levels were similar to their healthy relatives but higher than healthy Japanese individuals.[30] However, a study assessing the levels of ochratoxins in food samples collected from the same North Central Province of Sri Lanka found that they were below the recommended statutory maximum limit. Therefore, the role of ochratoxins in the causation of nephropathy is doubtful.[31]

Agrochemicals

In two rural agricultural communities of Nicaragua, population-based, cross-sectional study found that application of pesticide and chronic kidney had positive association with odds ratios of 4.80 (2.33–9.89).[32] Similar positive associations with odds ratio of 1.38 (0.90–2.11) and 5.5 (2.8–10.7) were also found in case control studies conducted among 997 volunteers and 499 hospitalized patients, respectively, in Nicaragua. However, in all three studies, the exposure was assessed using crude methods.[33,34] In Sri Lanka, positive association (2.34 [0.97–5.57]) between CKDu and pesticide applications was found by Jayasumana *et al.* in a hospital-based case control study with high internal validity.[35] In India, CKDu patients with GFR <90 ml/min/1.73 m^2 with or without proteinuria for 3 months had significantly higher blood concentrations of α–HCH, γ-HCH, total HCH, α-endosulfan, β-endosulfan, aldrin, p, p′-DDE, and total pesticides. The strength of association between all pesticides (third to first tertile) and CKDu was 2.73 (1.46–9.47).[36] In USA, out of 55,580 licensed pesticide applicators followed from 1993 to 1997, 320 developed ESRD. The highest category users had significantly increased hazard ratio (HR) as compared to nonusers, and there were significant exposure–response trends for the following pesticides: Alachlor HR = 1.51 [1.08–2.13], p for trend 0.015; Atrazine HR = 1.52 [1.11–2.09], p for trend 0.008; Metolachlor HR = 1.53 [1.08–2.13], p for trend 0.008; Paraquat HR = 2.15 [1.11–4.15], p for trend 0.016; Pendimethalin HR = 2.13 [1.20–3.78], p for trend 0.006.[37] In contrast to the above studies with positive association with pesticide exposure, there were no associations between CKDu and pesticide exposure in many other studies conducted globally.[12,38-41]

Infections

In a study conducted by Wijkstroem *et al.* in Sri Lanka**,** chronic glomerular and tubulointerstitial damage with glomerulosclerosis, glomerular hypertrophy, and mild to moderate tubulointerstitial changes were the key findings of kidney biopsies of 11 CKDu patients.[42] There were also findings indicative of active and chronic pyelonephritis with moderate to severe interstitial inflammation, which was similar to the findings observed among 19 male sugarcane workers in Nicaragua.[43] In a Sri Lankan study, eight out of 11 patients showed positive IgG antibodies for Hantavirus infection.[42] Similarly in another cross-sectional study from Sri Lanka assessing the levels of Hantavirus IgG antibodies among 132 CKDu patients and 200 healthy controls, 54.5% of CKDu patients were seropositive compared to 13.5% of healthy controls.[44] Based on the ecological and epidemiological evidence available in Central America, Murray *et al.* suggested that the rodent borne disease specifically leptospirosis may be the possible etiology for CKDu, particularly during the acute stage associated with febrile illness.[45]

Conclusion

From the available evidence, it is suggested that CKDu may be caused by multiple factors such as geographical, agriculture, heavy metals, heat stress, mycotoxins, agrochemicals, and infections. However, the above hypothesis has not been proved significantly. Therefore, large-scale studies with better methodologies need to be conducted to study the etiology and pathogenesis of CKDu. Simultaneously, efforts should be taken by all stakeholders in a coordinated manner to prevent and control the disease based on the available knowledge.

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Conflicts of interest

There is no conflict of interest.

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