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Update on Uncertain Etiology of Chronic Kidney Disease in Sri Lanka's North-Central Dry Zone

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ABSTRACT

INTRODUCTION This manuscript updates a review previously published in a local journal in 2012, about a new form of chronic kidney disease that has emerged over the past two decades in the north-central dry zone of Sri Lanka, where the underlying causes remain undetermined. Disease burden is higher in this area, particularly North Central Province, and affects a rural and disadvantaged population involved in rice-paddy farming. Over the last decade several studies have been carried out to estimate prevalence and identify determinants of this chronic kidney disease of uncertain etiology.

OBJECTIVE Summarize the available evidence on prevalence, clinical profile and risk factors of chronic kidney disease of uncertain etiology in the north-central region of Sri Lanka.

METHODS PubMed search located 16 manuscripts published in peer-reviewed journals. Three peer-reviewed abstracts of presentations at national scientific conferences were also included in the review.

RESULTS Disease prevalence was 5.1%–16.9% with more severe disease seen in men than in women. Patients with mild to moderate stages of disease were asymptomatic or had nonspecific symptoms; urinary sediments were bland; 24-hour urine protein excretion was <1 g; and ultrasound demonstrated bilateral small kidneys. Interstitial fibrosis was the main pathological feature on renal biopsy. The possibility of environmental toxins affecting vulnerable population groups in a specific geographic area was considered in evaluating etiological factors. Pesticide residues were detected in affected patients' urine, and mycotoxins detected in foods were below maximum statutory limits. Calcium-bicarbonate–type water with high levels of fluoride was predominant in endemic regions. Significantly high levels of cadmium in urine of cases compared to controls, as well as the disease's dose-related response to these levels, has drawn attention to this element as a possible contributing factor. Familial clustering of patients is suggestive of a polygenic inheritance pattern comparable to that associated with diseases of multifactorial etiology.

CONCLUSIONS Available data suggest that chronic kidney disease of uncertain etiology is an environmentally acquired disease, but to date no definitive causal factor has been identified. Geographic distribution and research findings suggest a multifactorial etiology.

KEYWORDS Chronic kidney disease, uncertain etiology, prevalence, clinical profile, risk factors, rural communities, paddy farming, environmentally acquired disease, Sri Lanka

INTRODUCTION

Mortality and morbidity due to chronic kidney disease (CKD) have been escalating over the past two decades in the north-central dry zone of Sri Lanka.[1,2] Disease burden is most pronounced in North Central Province (NCP) and is also present to a lesser extent in Uva and North Western Provinces. This zone has been a fertile ground for infectious diseases such as malaria and Japanese encephalitis in the past;[3,4] currently CKD is the zone's major public health problem. It has been debated whether this is a new disease entity, since no association was found with conventional risk factors. It has been labeled chronic kidney disease of uncertain etiology (CKDu). A study of CKDu emergence based on monthly hospital statistics from 1999–2004 showed increasing numbers of patients with CKD from 1980 through 2002.[5] The underlying cause of renal failure was unidentifiable in 82% of CKD patients seen at the renal clinic of NCP's main teaching hospital.[6]

NCP extends over 10,530 km^2 and is administratively subdivided into 30 secretariat divisions (DSD). Dry weather prevails most of the year; average annual rainfall is 1000–1500 mm during two monsoon periods.[7,8] A vast network of reservoirs feeds inland water to paddy cultivation in the province. NCP is a major rice cultivation area where two DSDs, Anuradhapura and Polonnaruwa, contribute 19–23% of total rice production in the country.[9]

CKDu affects rice farmers, a rural and disadvantaged population.[5] During the last decade several studies have attempted to identify CKDu risk factors and unravel its etiology.[1] All have been included North Central Province due to its high CKDu prevalence. In 2008, WHO joined Sri Lanka's Ministry of Healthcare and Nutrition to implement a research program (CKDu National Research Project Team), primarily to estimate CKDu prevalence and identify determinants.[10]

The objective of this review is to summarize updated available evidence on CKDu prevalence, clinical profile and risk factors in the north-central dry zone of Sri Lanka.

METHODS

A systematic literature search was conducted in PubMed to identify all potentially relevant publications through August 2013. The following keywords were used: *chronic kidney disease of uncertain etiology, CKDu*, *chronic kidney disease*, *kidney disease* and *North Central Province Sri Lanka*. Reference lists of original studies and review articles were also checked for further related articles. The search located 16 manuscripts published in peer-reviewed journals: 11 reviewed by the author for a previous local publication in 2012 (care taken to avoid self-plagiarism),[1] and 5 new papers published subsequently;[11–15] and 3 peer-reviewed abstracts of presentations at national scientific conferences.[5,16,17]

RESULTS

Prevalence Several population-based studies provide estimates of CKDu point prevalence. In 2011, Athuraliya found 5.1% (95% CI 4.2–5.9, n = 2600) in the population aged ≥20 years in Medawachchiya DSD, when persistent albuminuria was detected three times by dipstick and confirmed by sulfosalicylic acid, used as the screening tool.[18] Prevalence of CKDu was higher in men than in women but the difference was nonsignificant in multiple logistic regression. A 2011 community-based study in Medawachchiya, Padaviya and Rajanganaya DSDs assessed risk factors for microalbuminuria in 425 women and 461 men. Prevalence of

microalbuminuria for the total sample was 8.6% in men and 6.3% in women.[19] The CKDu National Research Project Team study used albumin–creatinine ratio ≥30 mg/g in an initial urine sample, confirmed at a repeat visit, to identify CKD patients. They reported an age-standardized prevalence of CKDu higher in women 16.9% (95% CI = 15.5%–18.3%) than in men 12.9% (95% CI = 11.5%–14.4%), but noted that more severe stages of CKDu were seen more frequently in men (stage 3, men 23.2% and women 7.4%; stage 4 men 22% and women 7.3%; p <0.001).[11]

Clinical profile CKDu is a slow, progressive condition that appears to start at younger ages but often is not detected until advanced stages. In Senevirathna's patient cohort, the proportion of early-stage CKDu was greater in the younger patient group, whereas higher proportions of advanced CKDu were seen in older groups.[12] There were no patients found in CKDu stage 4 (glomerular filtration rate 15–29 ml/min/1.73 m^2) in the younger group (<20 years), whereas almost 40% of the patients in the oldest age group (60–69 years) were in stage 4. The overall death rate in the same CKDu cohort was 5.3 per 100 patient-years and hypertension was identified as the leading determinant of disease progression. Self-reported hypertension was a significant predictor (p = 0.05) for disease progression, with a hazard ratio of 3.38 by multivariate Cox proportional model analysis for stage 1–4 patients.[12] It has previously been shown that patients with mild to moderate stages of CKDu were asymptomatic or had nonspecific symptoms such as backache or dysuria.[6] Patients' urine had no active deposits; 24-hour urine protein excretion was <1 g and ultrasound demonstrated bilateral small kidneys.[6]

Nanayakkara found that urinary excretion of alpha1-microglobulin was elevated in CKDu patients in the earliest stage compared with first-generation related controls residing in the same community and with Japanese controls, indicating that renal tubular damage occurs in a very early stage of CKDu.[13] In a retrospective analysis of renal histology, Wijetunga reported interstitial fibrosis as the main pathological feature in 2011 renal biopsies of patients with CKDu. Other changes such as interstitial inflammation and tubular atrophy were present in varying degrees but less common. Authors concluded that these changes were not specific to a single etiological agent.[14]

Risk factors Jayatilake's study concluded that female sex and age >39 years increased risk of CKDu. However, when separate logistic regressions were run for each potential risk factor, only occupation was significant; *chena* (vegetables and other crops) farming increased the odds ratio by 19.5% and working in paddy cultivation compared to chena cultivation decreased the odds ratio by 26.8%. Further, authors reported a family history of CKD in parents or siblings in 20% of individuals with CKDu.[11] Nanayakkara found familial clustering of patients suggestive of a polygenic inheritance pattern comparable to that associated with multifactorial diseases.[13]

In a case–control study in 2007, 183 CKDu patients seen at the renal clinic in the Anuradhapura Teaching Hospital (the province's main teaching hospital), were compared with a control group from the general medical clinic of the same hospital. Of risk factors evaluated, being a farmer (p <0.001), using pesticides (p <0.001), drinking well water at home (p <0.001) and in the field (p = 0.036), family history with CKD (p = 0.001), and past use of ayurvedic medicine (p <0.001) were significantly associated with CKDu. In multivariate logistic regression analysis, family history of CKD and past use of ayurvedic medicine were significant predictors of CKDu.[19] Most ayurvedic preparations are not standardized and may contain substances such as aristolochic acid, a known nephrotoxin.

Wanigasuriya argued that given the wide use of ayurvedic preparations in most of the country, higher prevalence of CKD in NCP is difficult to explain by this factor alone. Therefore, longterm use of ayurvedic medicine was further evaluated in a community-based study by the same investigators, finding no association with CKDu.[19] According to recently published data by Jayatilake, 0.4%, 1.8% and 0.6% of CKDu patients reported longterm use of medicinal plants, aspirin and NSAIDs respectively.[11]

Given CKDu's clinical profile, in order to assess etiologic factors, one consideration must be the possibility of environmental toxins affecting vulnerable groups in a specific geographical area. Exposures to various environmental toxins such as pesticides, microbial toxins and heavy metals have been explored as potential causes of kidney damage.

Pesticides A descriptive cross-sectional study was carried out in 2006 by Peiris-John to determine potential association between chronic renal failure (CRF) and low-level organophosphate pesticide exposure. Because red blood cell acetylcholinesterase is inhibited by organophosphates, it was used as an exposure marker; levels in farmers exposed to pesticides were significantly lower than in unexposed controls (p <0.05). Among CRF patients, red cell acetylcholinesterase levels were lower in the exposed than in the unexposed (p <0.05).[20] Added evidence pointing to involvement of nephrotoxic pesticide exposure in CKDu was provided by Jayatilake in the CKDu National Research Project Team study.[11] Pesticide residues were detected in urine from individuals with CKDu (n = 57). Detection frequency of 2,4-D, 3,5,6-trichloropyridinol, p-nitrophenol, 1-naphthol, 2-naphthol, glyphosate, and AMPA was 33%, 70%, 58%, 100%, 100%, 65% and 28% respectively. Urinary levels of isopropoxyphenol, 2,4,5-trichlorphenol and pentachlorphenol were below detection limits.[11]

Microbial toxins Ochratoxin A is a naturally occurring fungal toxin with carcinogenic and nephrotoxic properties. It is produced mainly by *Aspergillus* species in tropical climates and is present as a contaminant in many foods.[21] Ochratoxin A levels were tested in 98 food samples of 2 principal types of cereals (maize and rice) and 5 pulses cultivated and consumed by NCP residents.[22] Results indicated that ochratoxin A was a natural contaminant of cereals and pulses cultivated in these areas, but levels detected were below the statutory limit (5 µg/kg in raw cereal grains, including rice) recommended by the European food safety authority.[23] However, Desalegn's 2011 study in NCP demonstrated higher rates of urinary ochratoxins in CKDu patients and unaffected relatives, compared to Japanese controls, suggesting exposure to be common in the province. The small sample size (31) precluded assessment of association.[24]

Toxins produced by cyanobacteria can cause dermal, hepatic and neural toxicity in humans and nephrotoxicity in animals.[25] Also known as blue-green algae, cyanobacteria grow in calm nutrient-rich water, its blooms often found in reservoirs in CKDu-endemic areas of Sri Lanka. Dissananyake observed acute tubular necro-

sis in mice fed for one week with extracts of cyanobacteria isolated from two reservoirs in the endemic area.[16] In another study using geographic information system and geographic position system mapping, Jayasekara demonstrated that most affected villages in Medawachchiya and Padaviya are downstream from the reservoirs and irrigation canals.[15] They debated the possibility of seepage of contaminated water from canals and reservoirs into shallow wells. Based on these observations, authors identified cyanobacterium toxin as another potential environmental nephrotoxin present in the CKDu endemic area.[15,16]

Fluoride and drinking water hardness In endemic areas, water for drinking and cooking is obtained mainly from wells, both deep and shallow, while reservoirs are the main source of irrigation for paddy lands. Wanigasuriya concluded that subjects who drank well water in the field were approximately 2.5 times more likely to have microalbuminuria than those who did not.[26] Low CKDu prevalence was noted in communities where water for drinking and cooking came from natural springs (a few villages of Kebithigollawa DSD in the endemic area).[15]

Chandrajith further studied the geochemical properties of water. Electrical conductivity, alkalinity and fluoride levels were measured in well water samples from CKDu-endemic areas (Girandurukotte, Nikawewa, Medawachchiya and Padaviya DSDs) and from a nonendemic area (Wellawaya DSD).[27] Water samples were also tested from Huruluwewa, a nonendemic village in NCP, where people obtain drinking water from natural springs. Mean fluoride content in endemic CKDu areas of Girandurukottee, Nikawewa, Medawachchiya and Padawiya was 0.66, 1.21, 1.03 and 0.62 mg/L respectively. In Huruluwewa and Wellawaya, mean fluoride content was 1.42 and 1.05 respectively. Fluoride content of well water in both endemic and nonendemic areas was above the WHO-recommended level of 0.6 mg/L. Ca-bicarbonate–type water is predominant in endemic CKDu areas, whereas Na–K-nondominant anion type water is common in nonendemic areas. These observations led Chandrajith to propose that the cytotoxic properties of fluoride could be enhanced by a high of Ca^{2+}–Na^{+} ratio in ingested water.[28]

Heavy metals Bandara previously reported high levels of heavy metals—namely Cd, iron and lead—in five reservoirs in the CKDu-endemic areas.[29] Levels of Cd in water reported (0.03–0.06 mg/L) were much higher than the maximum contaminant level of 0.005 mg/L or 5 ppb recommended by USEPA.[30] However, these findings have been challenged by later studies. According to Jayatilake, Cd, lead and uranium levels in sources of drinking water consumed by individuals with CKDu (n = 99) were within acceptable limits. Arsenic was borderline or high in four samples (9.9 µg/L, 10.2 µg/L, 10.5 µg/L, 13.4 µg/L), but repeated analysis showed normal levels.[11] Findings of Chandrajith also indicated that Cd, arsenic and uranium levels in reservoirs and drinking water from wells were lower than the maximum contaminant levels recommended by USEPA, excluding the possibility of Cd, arsenic and uranium contamination of drinking water in the area.[27,28]

Bandara reported high Cd content in lotus rhizomes, rice and tobacco, and concluded that the provisional tolerable weekly intake of Cd, based on extreme exposure through rice and fish, was high in the area.[31] Other studies also showed higher mean Cd levels in lotus rhizomes and tobacco in endemic than in nonendemic areas (lotus: 0.413 mg/kg vs. 0.023 mg/kg; tobacco: 0.351 mg/kg vs. 0.316 mg/kg, in endemic versus nonendemic areas respectively).[11] However, Cd levels in rice in both endemic and nonendemic areas were below the allowable limit of 0.2 mg/kg in two other studies.[11,15]

Urinary Cd and arsenic are indicators of body burden and studies so far have given divergent results. The most comprehensive study of CKDu in Sri Lanka thus far by Jayatilake found urinary Cd significantly higher in CKDu cases than in controls, in both endemic and nonendemic areas.[11] Mean urinary Cd in CKDu cases was 1.039 µg/g creatinine (median 0.695, range 0.005–8.93); in controls from endemic areas 0.646 (median 0.18, range 0.005–5.13) and controls from nonendemic areas 0.345 (median 0.265, range 0.005–2.079). Levels were significantly elevated in CKDu cases compared to controls from endemic ($p < 0.001$) and nonendemic areas ($p < 0.05$). Sensitivity and specificity for urinary Cd concentrations were 80% and 53.6%, respectively (area under ROC curve 0.682, 95% CI 0.61–0.75, cutoff value ≥0.23 µg/g). Dose–response analysis showed that Cd exposure is a risk factor for development of CKDu: $p = 0.019$ for stage 3 and $p = 0.024$ for stage 4.

In the same study, no significant difference was observed in urinary arsenic levels in CKDu cases (mean 45.447 µg/g creatinine, median 26.3, range 0.4–616.6), compared to controls from endemic areas (mean 92.443, median 6.99, range 0.2–966.29), and controls from nonendemic areas (mean 56.572, median 42.025, range 5.38–350.28).[11] Further, authors reported low selenium levels in urine of CKDu patients. Urine concentrations of sodium, potassium, calcium, magnesium, copper, zinc, and titanium in CKDu cases were within normal limits. Previous studies by Chandrajith on a small number of patients failed to show elevated levels of Cd and other elements in urine of CKDu and control subjects.[27] Wanigasuriya estimated urinary heavy metal levels in CKDu-affected farmers from NCP and healthy farmers from Western Province, finding no significant difference in creatinine-normalized urinary concentrations of Cd, manganese, copper, nickel, arsenic and lead between the two groups.[17]

DISCUSSION

CKDu prevalence estimates vary in studies conducted in the north-central dry zone, in part because of differing screening methods used. The 5.1% prevalence reported with screening based on dipstick albuminuria is likely to be an underestimate because dipstick is not sensitive to low levels of albumin. The most recent study, where the screening criterion was 2 albumin-creatinine ratios of ≥30 mg/g reported an alarmingly high figure of 16.9%.[11] Urinary low molecular-weight proteins, such as alpha1-microglobulin, would be useful as a research tool to identify CKDu at very early stages. Lack of distinctive criteria for CKDu diagnosis was a problem in interpreting the various study results. In order to overcome this, in 2008, the Scientific Committee of the National CKDu Programme developed criteria to define CKDu: absence of a past history of diabetes mellitus, chronic or severe hypertension, snake bite, glomerulonephritis or urological disease; with normal HbA_1C (<6.5%); and blood pressure <160/100 mmHg untreated or <140/90 mmHg on ≤2 antihypertensive medications.[32]

Increased excretion of urinary alpha1-microglobulin in early stages of the disease indicates that tubular damage and tubu-

lar epithelial dysfunction occur early in disease progression.[13] Although histological features observed in renal biopsies do not indicate damage from a specific etiological agent, interstitial fibrosis may represent a low-grade toxic exposure.

In general, nondiabetic CKD prevalence is higher in women than in men, across age categories and ethnic groups.[33] This has also been true in Sri Lankan studies, but more severe stages of CKDu were seen more often in men.[11] This is consistent with Neugarten's meta-analysis of nondiabetic CKD progression indicating that male sex is associated with more rapid renal function deterioration and worse outcome.[34] Men in Sri Lankan CKDu endemic areas also have high prevalences of other risk factors—such as smoking, alcohol use and work in extreme weather conditions—that may have contributed to their disease progression; further studies are needed to explore this possibility.

Although low levels of red blood cell acetylcholinesterase in CKDu cases and pesticide residues detected in their urine are not sufficient to establish an etiological association, prolonged exposure to pesticides could play a role in either causation or progression of the disease.

Family history of CKD observed in CKDu does not necessarily suggest a single genetic defect but could be explained by shared environmental exposures in genetically predisposed individuals. Balkan endemic nephropathy has several features similar to CKDu, including disease predominance in farmers, familial aggregation of cases, and interstitial nephropathy seen in renal biopsy.[35,36] However, the increased incidence of tumors of the renal pelvis and ureter described in Balkan endemic nephropathy has not been detected in CKDu patients from Sri Lanka. Exposure to ayurvedic medicines could raise concerns about aristolochic acid nephropathy,[37] as *Aristolochia indica,* a creeper plant found in Sri Lanka and India, was used as herbal medicine in the ancient pharmacopeias. However the plant is not abundant in NCP and paddy contamination is unlikely.

Cyanobacterium toxin is likely present in water reservoirs but contamination of ground water in deep and shallow wells has not been demonstrated to date. Despite high urinary ochratoxin observed in the zone,[24] ochratoxin A in food samples cultivated and consumed by people in CKDu-prevalent areas was found to be below statutory maximum levels, indicating that this toxin was unlikely to be a risk factor.[22]

Geoenvironmental studies by Chandrajith illustrated a possible fluoride-mediated mechanism for renal damage in endemic areas. Chandrajith noted that Ca-bicarbonate–type water is predominant in endemic CKDu areas whereas Na-K–nondominant anion type water is common in the nonendemic areas. They postulated that Ca-bicarbonate–type water predominant in endemic CKDu areas enhances fluoride cytotoxicity. [28] Fluoride is widely distributed in the environment but is not a known nephrotoxin. There are few studies on fluoride-induced renal damage in humans, but animal studies have shown various histological changes in the kidney. [38,39]

Cd and arsenic have drawn attention from the time an environmental etiology was first postulated. Significantly high urinary Cd in CKDu cases compared to controls and the dose-related response reported by Jayatilake support a contributing role for Cd.[11] Arsenic levels have not been found to be significantly different in the two populations.

Cd nephropathy has been reported in people consuming Cd-contaminated water and in workers exposed to high levels of Cd.[40] Some studies suggest even relatively low levels of exposure increase risk.[41,42] Besides water and soil, recognized sources of Cd exposure include contaminated vegetables and ambient air in industrialized areas, as well as cigarette smoke. In Sri Lanka, high Cd levels have been seen in lotus roots, fish and tobacco, but have been inconsistent in rice. Superphosphate fertilizer is proposed as the most likely source of Cd in soil and vegetables.[29]

Smoking 20 cigarettes a day could result in average daily inhalation of 3.6–6 µg of Cd.[43] In the absence of industrial or water pollution in CKDu-prevalent areas, the significant urinary Cd observed may suggest that cigarette smoking and contaminated vegetables are factors responsible for low-level exposure to Cd. In a review that focused on studies of prevalence of Cd-related kidney dysfunction among populations in Cd-contaminated areas in China, dose-response relationships were shown between urinary Cd and renal damage markers, including beta-2-microglobulin, N-acetyl beta-D-glucosaminidase and albumin.[44]

This review highlights the limitations of epidemiology for establishing causation. The dose-response relationship observed with Cd supports a causal relationship; yet, there are many unanswered questions.[45] While scientists struggle to unravel the mystery, the continuing increase in CKDu burdens the health care system and affected families in the endemic area.

CONCLUSIONS

Although this review was limited by the heterogeneity of definitions and methodologies in the studies examined, no information has emerged since the previous review to contradict its conclusion that etiology of CKDu in north-central Sri Lanka is multifactorial, involving one or more environmental agents and possibly genetic predisposition in vulnerable populations. While the definitive cause is not known, weight of evidence suggests environmental exposure is key.

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