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The Prevalence of CKD of Unknown Etiology

By Dr. A. S. M. Julfekar Helal

Abstract- Chronic kidney disease (CKD)—or chronic renal failure (CRF), as it was historically termed—is a term that encompasses all degrees of decreased kidney function, from damaged–at risk through mild, moderate, and severe chronic kidney failure. Epidemics of CKD of uncertain etiology (CKDu) are emerging around the world. Highlighting common risk factors for CKD of uncertain etiology across various regions and populations may be important for health policy and public health responses. Prevalence of CKD of unknown (CKDu) etiology is being increasingly considered as an emerging etiology, especially in the developing countries, with environmental predisposition to hot humid climate, dehydration and toxic metal contaminations.

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I. Introduction

Chronic kidney disease (CKD) means your kidneys are damaged and can't filter blood the way they should. The disease is called "chronic" because the damage to kidneys happens slowly over a long period of time. This damage can cause wastes to build up in body. CKD can also cause other health problems.

The kidneys' main job is to filter extra water and wastes out of blood to make urine. To keep body working properly, the kidneys balance the salts and minerals—such as calcium, phosphorus, sodium, and potassium—that circulate in the blood. Your kidneys also make hormones that help control blood pressure, make red blood cells, and keep bones strong.

Causes of chronic kidney disease include diabetes, high blood pressure, glomerulonephritis, and polycystic kidney disease.[1-2] Risk factors include a family history of chronic kidney disease.[2] Diagnosis is by blood tests to measure the estimated glomerular filtration rate (eGFR), and a urine test to measure albumin.[3] Ultrasound or kidney biopsy may be performed to determine the underlying cause.[4] Several severity-based staging systems are in use.[5-6]

Screening at-risk people is recommended.[7] Initial treatments may include medications to lower blood pressure, blood sugar, and cholesterol.[8] Angiotensin converting enzyme inhibitors (ACEIs) or angiotensin II receptor antagonists (ARBs) are generally first-line agents for blood pressure control, as they slow progression of the kidney disease and the risk of heart disease.[9] Loop diuretics may be used to control edema and, if needed, to further lower blood pressure.[10-11] NSAIDs should be avoided.[12] Other recommended measures include staying active, and certain dietary changes such as a low-salt diet and the right amount of protein. Treatments for anemia and bone disease may also be required. Severe disease requires hemodialysis, peritoneal dialysis, or a kidney transplant for survival.[13]

Chronic kidney disease affected 753 million people globally in 2016: 417 million females and 336 million males.[1] In 2015 it caused 1.2 million deaths, up from 409,000 in 1990.[6]The causes that contribute to the greatest number of deaths are high blood pressure at 550,000, followed by diabetes at 418,000, and glomerulonephritis at 238,000.[6]

II. What is CKDu and who Gets it

CKDu or Chronic Kidney Disease of Unknown etiology/Uncertain cause is a type of chronic kidney disease that mainly affects marginalized agricultural communities in specific areas of the world where a large number of people develop an unexplained, deadly form of kidney disease.

The common clinical features of CKDu are impaired kidney function in the absence of diabetes, evidence of primary glomerulonephritis (either on renal biopsy or clinically), or structural abnormality. The limited number of kidney biopsies performed in affected persons show scarring of a type that might be the consequence of a wide range of insults.[6]

Although there have been numerous case reports, it is only now that evidence from population-based surveys is beginning to emerge showing that CKDu exists in India and Sri Lanka, [14-15] in addition to Central America.[1,9–11] It also may be occurring in other tropical/subtropical parts of the world, including Saudi Arabia, Egypt, and Senegal, but standardized data are not available for comparison. Valid comparisons cannot be made using renal replacement therapy registry data because of varying access. Therefore, valid prevalence estimates can currently be obtained only by identifying renal impairment in random population surveys.

III. Risk Factor of CKDu

CKD in general, and CKDu in particular, increases markedly with age. It is noteworthy that a high proportion of the participants had hypertension, diabetes, or proteinuria, in contrast with CKDu hotspots in Central America, and therefore it is more challenging to separate CKDu from CKD in this setting. Although CKDu is associated with agricultural work, it is not

Corresponding Author: Consultant, Department of Nephrology, Labaid Specialized Hospital, Dhanmondi, Dhaka, Bangladesh.
e-mail: sarwartopbright2019@gmail.com

particularly strongly associated with farming (odds ratio 1.39) or with pesticide use (odds ratio 0.85), unlike many studies in Sri Lanka.

The authors conjecture that "there might be a new etiological factor or multiple factors responsible." This is similar to findings in other cross-sectional studies in South Asia and Central America, which consistently find that increased risks, if they exist, occur primarily (but not exclusively) in agricultural populations, but that these do not seem to be clearly linked to exposures such as heat stress or pesticides. This may reflect the absence of any causal association, inadequacies with the exposure questions used, or the more general inadequacies of cross- sectional studies.[12]

In Asia, drinking water was the most studied risk factor, with heavy metals, agrochemicals, and food also frequently mentioned in many reports. Several studies report that drinking water in the dry region of Sri Lanka is very hard (high calcium), with elevated fluoride concentrations, salinity, and dissolved organic carbon and suggest that the interaction of magnesium and fluoride are potentially nephrotoxic.

Unique hydro geochemistry of Sri Lanka features hard or very hard water, and fluoride, iron, manganese, sodium, and lead have been re-ported to occasionally exceed applicable World Health Organization or U.S. Environmental Protection Agency drinking water standards. One geochemical study found that in regions where surface water recharged groundwater was commonly consumed, there was a low incidence of CKDu, while in regions where groundwater followed natural flow paths or had stagnant groundwater had increased incidence of CKDu, pointing to a potential geochemical source of contamination.

One study found trace levels of lead and high silicon concentrations in Indian ground-water, leading researchers to examine the potential cytotoxic risks of these chemicals. The resulting laboratory study showed that long-term exposure to both lead and silica at concentrations comparable to those found in the groundwater were found to be cytotoxic in in-vitro cyto-toxicity-assays on human-kidney-cell-lines.

In Anuradhapura, in the North Central Province of Sri Lanka, the local government has decided to prioritize clean drinking water in light of media coverage and research into the CKDu epidemic. Results from one interventional study in Sri Lanka show that replacement of drinking water supplies in CKDu patients with bottled water resulted in diminished disease progression; however, the study did not measure differences in water chemistry.

In farmers, the presence of increased dichlorodiphenyltrichloro- ethane (DDT) concentrations was associated with a greater drop in eGFR levels compared to those with low levels of DDT over 10 years. Exposure to pesticides has been implicated in the development of CKDu, but because of the cross-sectional nature of the studies and the widespread use of many nephrotoxic pesticides across the globe, it is difficult to attribute CKDu to pesticide exposure alone. Exposure to glyphosate, a weed killer that has been found to chelate metal ions and has been banned in many European Union countries because of concerns about linkages to cancer, has been proposed as contributing to the develop-ment of CKDu, especially with hard water.

In the presence of glyphosate, cadmium and lead are more likely to leach from soils in rice paddies. Contamination of naturally sourced fertilizers with heavy metals has been suggested as contributing to the development of CKDu in SriLanka, although at least one study has suggested that this factor may not be observed in endemic areas. A few studies suggest that pesticides may be involved in the development of CKDu in both Nicaragua and Sri Lanka. [13-14]

Other studies researched the presence of metals in other environmental media, such as soil and food. In some cases, arsenic, cadmium, lead, and mercury exceeded U.S. soil screening levels. Additionally, studies on environmental contamination in foods suggest that some may be consuming hazardous amounts of lead and cadmium in a typical diet of the region, while others could not find significant levels of heavy metals in food, water, or urine from the area Analysis of hair and toenail samples revealed a deficiency of selenium in both patients and controls, but no difference in cadmium or lead concentrations between CKDu patients and healthy individuals. Other environmental exposures have also been hypothesized as possible CKDu risk factors in Asia.

Mycotoxins, metabolites produced by fungi that grow in improperly stored rice, corn, groundnuts, wheat, and other products, have been linked with kidney disease and other adverse health outcomes, including cancer. Aflatoxins, ochratoxins, and fumonisins are several well-known classes of mycotoxins that have been characterized with respect to kidney disease. One study investigated the presence of mycotoxins in urine from CKDu patient, and another found elevated ochratoxins, aflatoxins, andfumonisins. Leptospirosis (or Weil's dis-ease), malaria, leprosy, and hantavirus have been suggested as potentialrisk factors contributing to CKDu in several endemic regions, suggesting that viral and bacterial infections may play a role in the development of CKDu.

Despite an increasing global awareness of CKD and CKDu, many of the risk factors remain unknown. In South Asia, family history, agrochemical use, and heavy metal exposures were studied most frequently, whereas altitude and temperature were studied only in Central America. However, many similarities also exist. Heavy metals, heat stress, and dietary exposures were reported in studies across all geographic regions, and family history, temperature, altitude, dietary exposure,

ochra-toxin A, herbal use, and snake bite were frequently reported in both South Asia and Central America.

Given the similarities and the differences observed in studies across the regions, the growing CKD burden may, in part, be driven by factors that are common across regions as well as unique within regions. Pathologic exposures can affect disease outcomes by interacting with a wide range of factors, including source emissions, transport and trans-formation, human contact, bioavailability, early expression of disease, and/or health effects.

In low-income countries, for example, rapid urbanization has led to poor sanitation, unplanned infrastructure, overcrowding, and environmental pollution. For CKD, these exposures may interact with other urban risk factors, such as high rates of noncommunicable and communicable diseases, to increase CKD prevalence Likewise, in rural, low–income areas, extreme poverty and agricultural-based economies expose people to other CKD risk factors, such as dehydration, snake bite, water contamination, heavy metals, and agrochemicals, which can also interact with noncommunicable and communicable diseases as well as genetic factors to increase CKD risk. As such, the regional variation in reporting of risk factors for CKDu may reflect a complex interplay between different global and regional exposures and local factors, such as environment and lifestyle. One example of regional variation in the reporting of risk factors for CKDu was observed with dehydration. Al-though dehydration is increasingly being posited as a potential etiologic factor for CKDu in endemic communities, assessment of the associations between dehydration and CKDu across studies was limited by in consistent reporting of the measurements for assessing dehydration.

For example, whereas all studies that measured variation in altitude and seasonal temperature reported a significant association between dehydration and CKDu, studies re-porting heat stress infrequently reported an association between dehydration and CKDu. This highlights the importance of designing standardized measurements to consistently and comparatively assess the role of dehydrationin the etiology of CKDu across the world. Additionally, genetics may also play a role in the observed regional heterogeneity in the reported epidemiology of CKDu. Genetic differences in ethnicities are known to have a strong effect on the prevalence and risk of progression of CKD.

In the United States, for example, Americans of African descent who carry the APOL1 genotype have higher rates and faster progression of CKD, especially when exposed to other augmenting factors, such as diabetes and hypertension. In India and Sri Lanka, there are specific polymorphisms and single-nucleotide mutations that have been associated with CKDu in some endemic communities, and in the Balkan states, particular chromosomal aberrations have been associated with Balkan Endemic Nephropathy. Therefore, more studies should be conducted to explore the role of genetic predisposition in the CKDu disease mechanism.

Additionally, the causal association between heavy metals and CKDu is not well established, and but some studies observed significant variability in the reported associations. For example, cadmium was inconsistently reported to be associated with CKDu, whereas arsenic was consistently associated with CKDu. Another study also observed regional heterogeneity in the reporting of heavy metals as a risk factor for CKDu. Only one study from Central America reported heavy metals, whereas six studies from South Asia reported it. It is likely that heavy metals do play a role in the development of CKDu in endemic areas, where levels are often present in the microenvironment and multiple other risk factors coexist. However, because the microenvironment and human levels of heavy metals from CKDu-endemic regions have been reported to be below the upper limits of detection, exploring mechanisms of interaction between heavy metals and other risk factors may be important in advancing CKDu research.

Table-1: Five most frequently studied CKD of uncertain etiology risk factors by region

CKDu Risk Factors by Region	
South Asia (n=11; 42%):	n
Heavy metals	6
Occupation (farmer)	6
Family history	5
Agrochemical use	4
Smoking	4
Central America (n=8; 31%)	n
Age	7
Men	7
Agrochemical use	6

Occupation (farmer)	5
Heat stress	3
Other regions (n=7; 27%)	n
Body mass index	3
Heavy metals	2
Age	2
Dietary exposure	1
Heat stress	1

However, still do not know, at least on a global level, who gets this disease, or even if the disease is the same in different parts of the world.[15-17]

This lack of basic epidemiological information also has important implications for health care. World Kidney Day 2019 has a theme of "health care access for all," but health care access cannot be provided for a disease that is unrecognized, undiagnosed, and (even when diagnosed) often un- treated. CKDu is clinically silent in the early stages and, in many of the affected areas, carries a poor prognosis. It is usually diagnosed late, and no data are available on factors predicting progression. Renal replacement therapy is un-available in many low- and middle-income countries, and even if present, it is often in accessible to most of the population, meaning that end-stage renal disease is usually fatal. In addition to the young lives lost, CKDu has a substantial negative impact on social and economic development of affected countries, through jeopardizing the economic development of the affected communities, and straining the poorly resourced health systems of the affected countries.

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