

CKD of Unknown Cause: A Global Epidemic?



Neil Pearce¹, Ben Caplin², Nalika Gunawardena³, Prabhdeep Kaur⁴, Cristina O'Callaghan-Gordo^{1,5,6,7} and Thilanga Ruwanpathirana⁸

¹Department of Medical Statistics, London School of Hygiene and Tropical Medicine, London, UK; ²Centre for Nephrology, Department of Renal Medicine, Division of Medicine, University College London, London, UK; ³World Health Organization, Country Office, Colombo, Sri Lanka; ⁴Department of Non-communicable Diseases, National Institute of Epidemiology (Indian Council of Medical Research), Chennai, India; ⁵ISGlobal, Barcelona, Spain; ⁶Universitat Pompeu Fabra (UPF), Barcelona, Spain; ⁷CIBER Epidemiología y Salud Pública (CIBERESP), Barcelona, Spain; and ⁸Epidemiology Unit, Ministry of Health, Colombo, Sri Lanka

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World Kidney Day is an appropriate time to reflect on the epidemics(s) of chronic kidney disease (CKD) of undetermined cause (CKDu) that are affecting agricultural communities in Central America, South Asia, and possibly other parts of the world.^{1–4} The cause(s) of CKDu remain to be established, with heat, pesticides, water (including heavy metals), infections, or other factors being suggested as the primary cause(s). However, we 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. 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 untreated. 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 unavailable in many low- and middle-income countries,⁵ and even if present, it is often inaccessible 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.

What Is CKDu and Who Gets It?

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,^{7,8} in addition to Central America.^{1,9–11} It also may be occurring in other tropical/subtropical parts of the world, including Saudi Arabia,¹² Egypt,¹³ and Senegal,¹⁴ 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. Thus, we have recently established a partnership that has developed a common protocol to estimate distributions of renal function in disadvantaged communities globally: the Disadvantaged populations estimated glomerular filtration rate epidemiology study (DEGREE).¹⁵

What Does the Article by Tatapudi *et al.* Add?

The article by Tatapudi *et al.*¹⁶ of a population-based survey in the Uddanam region of Andhra Pradesh in India, in this issue of the journal, is a welcome addition to the literature on CKDu. It adds to other recent evidence from population-based surveys in India¹⁷ and Sri Lanka,⁸ and confirms that CKDu occurs in South Asia as well as in Central America. The importance of this should not be underestimated. It is only by population-based studies of this type that we can really know who gets this disease

Correspondence: Neil Pearce, Department of Medical Statistics, Faculty of Epidemiology and Population Health, London School of Hygiene and Tropical Medicine, Keppel Street, London WC1E 7HT, UK. E-mail: neil.pearce@lshtm.ac.uk

globally; this is not only crucial in public health and clinical terms, but is also an essential first step in discovering the causes of CKDu.

Before discussing the findings, several limitations of the study should be noted. As with all cross-sectional studies of this type,¹⁵ it is not measuring the prevalence of CKDu, because it involves a “one-off” measurement of eGFR, whereas 2 measurements are required to confirm the chronicity of any form of CKD. A related issue is that eGFR calculated from serum creatinine is a function of ethnicity¹⁸ and can also vary with exercise, muscle mass, and meat consumption. In particular, it has been previously suggested that we are likely to overestimate kidney function in South Asian individuals,^{18,19} and therefore that prevalence estimates in India and Sri Lanka may be falsely low. However, although these are issues for clinical diagnosis, and for comparisons between different regions of the world, they are unlikely to be major issues in subgroup comparisons within a particular region.¹⁵ Perhaps a more significant issue is that Tatapudi *et al.*¹⁶ appear to provide no information on the calibration of creatinine, and their definitions of key biomarkers are somewhat nonstandard (e.g., the protein-creatinine ratio cutoff of 0.2, the definition of “long-standing hypertension,” which requires this to have existed for more than 5 years); these issues may lead to the inclusion of some patients with glomerulonephritis or other known causes of CKD, thus overestimating the prevalence of true CKDu. For example, in the Sri Lankan surveys,⁸ the prevalence of “suspected CKDu” dropped from 10.7% to 6.7% when more restrictive exclusions for hypertension were used. A further concern is that the sampling methodology does not clearly indicate whether population enumeration was carried out, the

criteria used for defining the sampling frame, and the sampling procedures. The concern is that there may be greater participation from those affected with CKD, which may lead to prevalence being overestimated. These methodological issues are unlikely to bias subgroup comparisons, but they do make comparisons with other studies in the same region^{8,17} more difficult.

So apart from confirming the presence of CKDu, what else does the study of Tatapudi *et al.*¹⁶ contribute? As with other comparable studies,^{8,17} the prevalence of 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 particularly strongly associated with farming (odds ratio 1.39) or with pesticide use (odds ratio 0.85), unlike many studies in Sri Lanka.²⁰ 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^{8,17} and Central America,²¹ 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.⁹ This may reflect the absence of any causal association, inadequacies with the exposure questions used, or the more general inadequacies of cross-sectional studies. In fact, a study in Central America^{21,22} involved follow-up (after an initial cross-sectional study), and identified a distinct subgroup experiencing rapid decline in kidney function,

although the risk factors for this decline were still difficult to identify.

Where Next for CKDu?

So where next for CKDu? There are 2 immediate conclusions that can be drawn from the study of Tatapudi *et al.*¹⁶

First, it is urgent to discover which parts of the world are experiencing endemic/epidemic CKDu. In some commentaries there have been assumptions that the condition is either confined to a particular area, with local risk factors playing a key role (hence the use of “local” names, such as Meso-American nephropathy²³ or Uddanam nephropathy²⁴), or that there is a global epidemic with common risk factors across regions.²⁵ The reality is that no one knows, and that global health policy cannot be based on anecdotal reports of individual cases, particularly for a “disease of exclusion,” such as CKDu, where there is always a risk that apparent cases of CKD may in fact be due to undiagnosed diabetes or other established causes of kidney disease. What is required is population surveys in different parts of the world using standardized methods.¹⁵ Until these have been done, we cannot say more than that CKDu exists in Central America and South Asia, but that we cannot say much about the rest of the world. Perhaps there is a global epidemic that will require major health system resources and raise major issues of “health care access for all,” or perhaps these are regional rather than global problems. We simply do not know. We need more surveys and publications like that of Tatapudi *et al.*¹⁶

Second, although prevalence surveys are an essential first step, they need to be followed by more intensive cohort studies in “at-risk” populations,^{21,22} as recommended by Tatapudi *et al.*¹⁶ It is

only through more intensive data collection of this type that we can make progress on discovering the cause(s) of CKDu, and whether the “epidemics” in Central America and South Asia involve common causes, or separate local causes.

DISCLOSURE

All the authors declared no competing interests.

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