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**Let's take the heat out of the CKDu debate:
more evidence is needed**

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There is considerable controversy about the causes of the epidemics of Chronic Kidney Disease of undetermined cause (CKDu) which are affecting agricultural communities in Central America, South Asia, and possibly other parts of the world. In this editorial, we argue that currently none of the suggested hypotheses have enough evidence, either for or against them, to draw firm conclusions.

What is CKDu and who gets it?

The common clinical features of CKDu are impaired kidney function in the absence of diabetes, primary glomerular nephritis, or structural abnormality. CKDu exists in Central America[1] and South Asia (India and Sri Lanka)[2, 3], and mainly affects male rural agricultural workers. It may also be occurring in other tropical/subtropical parts of the world, but standardized data are not available for comparison[4]. We will therefore focus on the evidence from Central America and South Asia.

CKDu was first described in Central America in 2002[5], and in the rural population of the North Central Province of Sri Lanka in 2000[6]. However, the estimates in Sri Lanka are not comparable with those from Central America, as in the Sri Lankan prevalence studies to date, serum creatinine has only been performed in those with proteinuria, i.e. an albumin-creatinine ratio (ACR) ≥ 30 mg/g, whereas CKDu typically presents with either no or low-grade proteinuria in Central America[7]. Other potential problems of international comparisons arise because the estimated Glomerular Filtration Rate (eGFR) calculated from the serum creatinine is a function of ethnicity[8], exercise, muscle mass and meat consumption. Therefore, valid prevalence estimates can currently only be obtained by identifying renal impairment in random population surveys[4].

Causes of CKDu

Perhaps the most clearly established risk factor in both Central America and South Asia, is that CKDu is more common in agricultural communities[9]. In Central America, CKDu occurs frequently in sugar cane workers, but also in other occupational groups, including other agricultural workers, fishermen, miners, and construction workers[10]; it also occurs at a lower frequency in women, most of whom have not worked in agriculture. Furthermore, in a recent study in Nicaragua we found that marked decline in kidney function was occurring in a subgroup of participants, whereas the rest of the participants were maintaining normal

kidney function[11]; the key exposures in this high-risk subgroup are yet to be identified, but it involved a wide range of agricultural jobs (not just sugarcane), and also involved women who did not work in agriculture.

A large number of specific causes, related to agriculture, have been suggested for CKDu. Heat/dehydration, infection/inflammation and pesticides are the main hypotheses that have been proposed for Central America, whereas in South Asia the emphasis has been on the possible roles of water contamination/metals and/or pesticides.[12] Other possible causes include non-steroidal anti-inflammatory drugs (NSAIDs), population genetics and alcohol [1]. However, a recent systematic review in Central America found that the only risk factors with strong evidence were male sex, family history of CKD, high water intake, and low altitude; data on the other hypotheses which have been proposed, including self-reported heat stress, pesticide exposure, alcohol, and NSAIDS, have little or no support from epidemiological studies[1, 13].

Each of these proposed causes is discussed in detail below.

Heat stress and dehydration

Heat stress and dehydration has become the favoured explanation for the CKDu epidemic in Central America. The report of the 2015 Regional Workshop[14] concluded that “there is growing evidence for a causal role of strenuous work, heat and insufficient rehydration as risk factors for MeN”, although it was also noted that “it is also quite possible that other factors play a role in the disease, perhaps in combination with heat stress and dehydration” and that “exposures to specific agro-chemicals or other yet-unknown toxins need further evaluation”.

The case for heat stress nephropathy has been summarised in a recent review[15], which argues that “recurrent heat exposure with physical exertion and inadequate rehydration can lead to CKD”, and that the excesses in male sugarcane workers arise because they work in extreme conditions of heat exposure and work intensity, as do agricultural workers in many other countries[16]. The authors argue that similar patterns have been observed in South Asia, although heat stress and dehydration are not the currently favoured causal hypotheses in this region [17]. In response, Herath et al [9] give the case against heat-stress nephropathy. They argue that there is sparse evidence of acute kidney injury (AKI) among

high risk manual workers, and little evidence that repeated moderate elevations in serum creatinine will lead to CKD, that the animal studies involve extreme forms of AKI which are not observed in workplace-based epidemiological studies, that CKDu is not seen in workers exposed to heat in most tropical regions, that the disease is seen in people not exposed to heat stress in the affected regions, and that in general there is inadequate evidence for it being the initiating and/or main cause of a major global epidemic of CKDu. Similarly, Ordunez et al[18] have concluded that the overall time trends and mortality patterns for CKD in Central America suggest that the heat/dehydration hypothesis cannot fully explain the epidemic. VanDervort et al[19] have reached similar conclusions regarding the spatial distribution of CKDu in El Salvador.

Heat stress/dehydration is the only hypothesis for which there is also evidence from an intervention study. This was conducted under extremely difficult conditions in El Salvador[20, 21], resulting in great difficulties in following the non-intervention comparison group. The study clearly shows a reduction in heat stress and cross-shift changes in serum creatinine in the intervention group, but the differences between the intervention and comparison groups are small and not statistically significant; furthermore, both groups showed a reduction in eGFR over time which is consistent with a seasonal effect, which has also been observed in the neighbouring country of Nicaragua[11].

Pesticides

Pesticides have been proposed as the cause(s) of CKDu in both Central America and South Asia, although they have perhaps received more attention in the latter context [22]. Given the link with agricultural communities, it is not surprising that pesticides have been suggested as possible causes, particularly since many pesticides in common use are known human nephrotoxins[23]. Nevertheless, the 1st International Mesoamerican Nephropathy (MeN) Workshop in 2012 concluded that pesticides were an unlikely cause of CKDu, and that heat stress and dehydration were the more likely key etiologic factors[24]. Our own systematic review also found little evidence that pesticides were the main cause of CKDu in Central America[1]. More generally, Valcke et al[25] identified 21 relevant analytic studies, but concluded that most had inadequate information on pesticide exposure. The four studies with stronger designs, from Sri Lanka, India and the USA, all showed clear associations, but for different pesticides in each study, and three of these were in areas

without CKDu epidemics. They conclude that pesticides can cause AKI, but that there is no clear evidence that they are causing the CKDu epidemics. Jayasumana et al[26] have hypothesized a joint effect of glyphosate and metals in water in Sri Lanka, but no associations have been seen in other regions; glyphosate is widely used in Central America, but one study involving six-month follow-up did not show kidney effects in pesticide applicators[27].

Metals and other contaminants in water

Metals and other contaminants in water have received particular attention as possible causes of CKDu in South Asia[28], particularly with regards to the possible roles of arsenic, cadmium, fluoride and aluminium. However, studies in both Central America[29] and South Asia[23] have consistently found low levels of these contaminants in water and/or urine in CKDu-affected populations. The potential role of silica has been of particular concern in India[30] although these findings have yet to be replicated. Jayasumana et al[31] hypothesized that arsenic was the likely cause of CKDu in Sri Lanka, but studies have generally not found high levels of arsenic in drinking water and/or urine[23]. Similarly, fluoride in water has been raised as a possible cause of CKDu in Sri Lanka[23], but this hypothesis remains highly speculative.

Infection/inflammation

Evidence for an infective/inflammatory cause rests on seroprevalence studies in those affected [10] and case series from both Sri Lanka and Nicaragua describing an acute febrile syndrome in patients presenting to health services with renal dysfunction[32-34]. The acute inflammation observed on renal biopsy in these studies is certainly consistent with a response to an infectious aetiology or alternative inflammatory precipitant. However, whether these cases represent “Clinical Evidence of Acute Mesoamerican Nephropathy”[33], as described in the Nicaraguan studies, or rather AKI in response to an unspecified infectious illness occurring in those at high risk of renal decline due to an existing CKDu of a non-infectious cause cannot be distinguished with this type of study design. More recently, there has been evidence linking hantavirus infection to CKDu cases in Sri Lanka[35] and it has been suggested that the excess mortality among children and

adolescents indicates a role of early and long-term exposure to infectious and/or other toxic agents[18, 36].

Other possible causes

Evidence regarding other possible causes is largely anecdotal. These include NSAIDs, alcohol, and intake of fructose-rich soft drinks. Currently, there is little good evidence from population-based studies which would allow these hypotheses to be either confirmed or rejected[23].

Multifactorial hypotheses

Finally, several reviews[9, 15, 25, 36, 37] have concluded that the cause(s) of CKDu are likely to be multifactorial, basically because no single cause has been discovered, and therefore it is possible that two or more of the various possible causes may work in combination. In fact, most diseases are multifactorial[38], but epidemics usually are not. For example, the epidemics of lung cancer in the 20th century were caused by increased exposure to just one of the causes (i.e. smoking), whereas other contributing factors (e.g. genetics) had not changed, and therefore cannot account for the 20th century epidemics. The likelihood of a single factor playing a key role in the CKDu epidemics, is perhaps enhanced by our recent findings from Nicaragua, in which rapid decline in eGFR was confined to a subgroup of the population[11]. It is also noteworthy that there are well-known examples where the cause(s) of a particular epidemic, or of regional differences in disease risk, took some years or decades to be discovered, and involved several competing hypotheses.

One of the most interesting examples is the epidemic of Balkan Endemic Nephropathy (BEN)[39], which is essentially another type of CKDu. Over a period of 50 years, the hypotheses on the causes of BEN included mycotoxins, metals, viruses, and trace-element insufficiencies[39]. It now seems clear that the main cause was chronic dietary exposure to aristolochic acid (AA) which is the principal component of *Aristolochia clematitis* which grows as a weed in wheat fields in the Balkans[39]. Thus, our lack of success in discovering the cause(s) of CKDu to date does not mean that the disease is multifactorial; it is still possible that one of the hypothesized risk factors, or something we have not yet thought of, is the key driving factor behind the epidemics.

Where to from here?

So even if we don't know the cause(s), why don't we just intervene anyway? The main possible interventions would involve better working conditions, lower pesticide exposure, prevention of infection and cleaner water supplies. All of these should be supported because they will improve working conditions and prevent occupational disease in general, even if their likely impacts on CKDu are currently uncertain. An equally high priority is better research taking an agnostic approach. Clearly, a number of different research methodologies will ultimately contribute to solving this mystery, but in the table we suggest a few key epidemiological questions that address the missing pieces of the jigsaw. What is needed is not further studies or reviews which try and sell the case that a particular risk factor, or combination of risk factors, is the culprit. What is needed instead is smart epidemiology, in which we try and distinguish between the various hypotheses, and develop new ones.

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Table: key epidemiological questions about CKDu

- Who gets this disease? Does it occur in all tropical/subtropical regions of the world, or only in some?
- Does this look like the same disease in different parts of the world? i.e. are we experiencing a single epidemic in different parts of the world, or are different epidemics occurring in parallel?
- What is the prevalence in various parts of the world which have exposures to some of the risk factors, but not others, e.g. in areas which are hot and involve strenuous work, but not pesticide exposure, and vice versa?
- Within at risk regions, which population subgroups are most at risk? Is it always rural male agricultural workers (and sugarcane workers in particular)?
- Within the at risk populations, what determines who suffers from kidney function decline, and can we identify them (e.g. with appropriate biomarkers) prior to the development of established CKD (at a time point when exposure assessment or kidney biopsy might provide more insight)?