

# Is an Environmental Nephrotoxin the Primary Cause of CKDu (Mesoamerican Nephropathy)? Commentary

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The environmental nephrotoxin component as the etiology for CKD of unknown cause (CKDu) has been elegantly discussed in a debate by De Broe (pro) (1) and Wesseling (con) (2) in this issue of *Kidney360*. The etiology of CKDu has been a topic of enormous controversy, and it seems that this same controversy has characterized this disease. Although it is currently unclear whether there is a unified underlying cause, these conditions have been collectively termed CKDu, but various names have emerged. They include the following: CKD of nontraditional cause, Mesoamerican nephropathy, chronic interstitial nephritis in agricultural communities, and kidney disease of unknown cause in agricultural laborers. I will refer to CKDu in my piece as it is a preferred and neutral term. It is evident that simple things, such as naming the disease or establishing a definition for CKDu, have generated enormous difficulties that create obstacles to the detection and optimal treatment.

I would argue, however, that we do have consensus in some CKDu areas. First, we agree that those affected by CKDu do not have traditional risk factors or underlying conditions that lead to CKD, such as older age, diabetes mellitus, hypertension, GN, or structural kidney disease. In instances where histopathology is available, the predominant feature is tubular atrophy/interstitial fibrosis (3,4). Unfortunately, kidney biopsy is available for only a minority of the cases, and we have to accept different levels of uncertainty when defining CKDu. Second, there is little doubt the disease occurs in disadvantaged populations. During the last decades, it has been increasingly recognized that CKD is more frequent and has poorer outcomes among populations or communities considered “disadvantaged” in both the developed and developing world (5–9). Such communities include “ethnic, socioeconomically deprived, and other minority groups that are at greater risk of developing CKD,” according to the International Society of Nephrology (10). The causes of CKD in disadvantaged populations are varied and reflect exposures to environmental, socioeconomic, and other factors that contribute to a reduction in nephron mass over time. In any one individual, perinatal and nutritional factors, exposure to toxins and infections, heat stress, and dehydration may all contribute to the development of CKD. CKDu is clearly

one of the conditions that is over-represented in disadvantaged populations.

Third, we can agree that apart from being more frequent, kidney disease among disadvantaged populations tends to be underdiagnosed. When detected, access to care is limited and frequently, suboptimal (9). Irrespective of the underlying cause of CKD, the combination of those two factors—underdiagnosis and suboptimal treatment—contributes to poor clinical outcomes. Moreover, the development of ESKD in communities in which access to RRT is limited or nonexistent forces households to incur substantial “out-of-pocket” expenses, perpetuating the poverty cycle (11).

Fourth, we can probably agree that the existing evidence in CKDu is still insufficient and that urgent research is needed in order to move the field forward. At this point, I would argue against the fact that we have “strong” evidence to support any etiology. The word strong should be avoided because associations can be found, but causality is not warranted. At best, the current evidence may help with hypothesis generation and future study design. For instance, finding large dysmorphic lysosomes in proximal tubular cells from biopsies in agricultural workers may suggest a tubular toxicity mechanism similar to what has been seen with calcineurin inhibitor damage (12); however, pesticides or heavy metals were not directly measured in any of these subjects. Likewise, intervention studies where water, shade, and rest have been implemented in order to mitigate the deleterious effects of heat stress on kidney function have been only partly effective in reducing kidney injury biomarkers but have not yet demonstrated that CKD can be prevented (13,14).

Improving the quality of the current evidence should be a priority. We have worked with the International Society of Nephrology and have recommended the following major steps in order to strengthen the evidence on the field: (1) pursue longitudinal studies and make provisions for biorepositories, (2) reinforce the capacity for obtaining kidney biopsies as well as diagnosis and investigation of pathogenesis, (3) create an open-access database to ensure transparency and collaboration, (4) partner with participants and community leaders in study design and ensure return of study results to participants, and (5) build long-term

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relationships between international and local researchers that emphasize fairness and trust (15).

Finally, given the complexity and systemic nature of this problem, the required interventions are interdisciplinary and multidimensional. Therefore, it is not only a matter incumbent to the medical community. Only global-scale efforts involving multiple stakeholders will be able to close the observed gaps in kidney care that disadvantaged populations experience. Key partnerships between governments, nongovernmental organizations, researchers, and clinicians are paramount to achieve an improvement in outcomes. The World Health Organization has established sustainable health goals that are only possible with a multidisciplinary approach.

In conclusion, CKDu remains a topic of great debate with large knowledge gaps. Current evidence is limited, and observations at this point may be only hypothesis generating. Identifying the major risk factors in each community is paramount to maximize the efficacy of any intervention. Inequity in health is the cornerstone of the observed disparities in CKDu burden among disadvantaged populations. It is a moral imperative to solve the existing disparities, especially given the evidence that in some cases, there is lack of access to RRT. Further research and strong collaborations between different entities are urgently warranted in order to better characterize the disease etiology in different regions of the globe and design well conducted interventional trials that may lead to improved outcomes for this vulnerable population.

#### Author Contributions

M. Madero wrote the original draft and reviewed and edited the manuscript.

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See related debates, “Is an Environmental Nephrotoxin the Primary Cause of CKDu (Mesoamerican Nephropathy)? PRO” and “Is an Environmental Nephrotoxin the Primary Cause of CKDu (Mesoamerican Nephropathy)? CON,” on pages 591–595 and 596–601, respectively.