Challenges and opportunities in interventions to address chronic kidney disease of unknown origin (CKDu): Report from the Intervention Workgroup of the International Society of Nephrology Consortium of Collaborators on CKDu

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Introduction

Chronic kidney disease of unknown origin (CKDu) is a progressive tubulointerstitial nephropathy reported principally in agricultural communities, specifically manual laborers in dry, lowland regions of Central America, Sri Lanka and Southern India.[1] Further research may reveal whether it is present, but unrecognized, in other regions, including in parts of South East Asia, Africa and the United States.

The disease was first described at the start of the century,[1] and while scientists largely agree on common clinical characteristics, much of the pathophysiology remains unclear. One leading hypothesis presently is occupational exposure to recurrent heat stress; other hypothesized factors include environmental toxins, genetic predisposition, and dietary or pharmaceutical exposures, or some combination thereof. Persisting uncertainty has led researchers to focus on questions of pathogenesis and epidemiology. However, ongoing disease burden, especially in the context of a lack of access to effective treatments, and the potential for affected populations to experience research fatigue and disillusionment, demands that efforts to prevent and treat CKDu are undertaken as a priority. Interventional study designs that test preventative strategies and focus on addressing the concerns of affected populations may offer a path forward. While challenging to design when uncertainty around etiology persists, interventional studies can be a strong test of a causal hypothesis and such studies may also advance our understanding of CKDu pathophysiology while potentially benefiting the affected populations.

In 2016, The International Society of Nephrology convened the International Consortium of Collaborators on Chronic Kidney Disease of Unknown Etiology (i3C), which has reported on disease detection strategies [2] and on methodologies to elucidate the cause of CKDu.[3] Recognizing the urgent need for preventative and disease-modifying therapies, i3C presents this commentary as a starting point for researchers seeking to mitigate the burden of CKDu. We acknowledge the challenges

inherent to interventional research in this area, while emphasizing the need for unbiased evidence and the various study designs and other solutions that can be employed.

Challenges in interventional research in CKDu

Interventional studies can be directed at specific levels of disease prevention: primary prevention studies identify hazard(s) to prevent disease onset, secondary prevention studies identify early evidence of disease (usually by screening) at a stage where intervention(s) can cure or prevent further progression, while tertiary prevention studies attempt to reduce the impact of illness or injury and associated disability.

The conduct of interventional studies targeting CKDu (at any level of prevention) faces substantial – though not insurmountable – challenges. Affected communities are often marginalized and have minimal available health resources. In addition, the natural history of CKDu is poorly understood and potentially important exposures could occur early in life and/or in several different environmental domains. Furthermore, identification of appropriate surrogate markers for disease progression other than decline in GFR necessitates long follow-up times which can be difficult in low-resource community population studies. However, short-term (absolute and relative) changes in serum creatinine or GFR have been evaluated in the context of CKDu. This could be particularly important given that one purported causal mechanism is recurrent episodes of severe acute kidney injury (AKI); making prevention of AKI a key potential target of intervention. Note that while AKI (defined by limited changes in serum creatinine or urine output) may offer a shorter-term endpoint for interventional studies, the detection of AKI may be challenging in community populations.

To date, three prospective, non-randomized, interventional trials have been published, finding reductions in decline in kidney function over periods ranging from 3 weeks to 18 months. Two are examples of primary prevention with a package of health and behavioral education [Box 1],[4] and improved working conditions.[5] The other is a tertiary prevention study of replacement of usual water source with bottled water for those with CKDu.[6] A randomized tertiary prevention trial,

comparing enalapril to placebo in proteinuric CKDu, demonstrated reduced proteinuria with no difference in decline in eGFR over 12 months,[7] and a randomized trial of allopurinol to reduce the risk of kidney and cardiovascular outcomes, is underway.[8] These studies demonstrate the need to involve workers, employers, healthcare services, and communities in study design, set-up, and implementation. Clearly, with appropriate design to address sources of bias, interventional studies in CKDu can be conducted and may generate evidence to inform changes in workplace practice and future research.

Interventional study design considerations in CKDu

All interventional study designs have strengths and weakness (Table 1). The archetypal parallel group individually randomized controlled trial (RCT) can be applied to CKDu populations [Box 2], but often is neither feasible nor ethical. The key consideration in the selection of an intervention study design is the nature of the intervention being tested. Many potential primary or secondary prevention interventions for CKDu, such as changes to workplace practice, provision of clean drinking water, environmental protection, personal protective equipment use, and education, are most efficiently applied to communities, and would be difficult to ethically deny a 'control' group. Furthermore, applying such interventions to individuals may be impractical, not be acceptable to the community members, or may be thwarted by sharing of information and behaviors between individuals resulting in contamination of the original random allocation.

Thus, cluster-randomized designs can be a solution for interventions applied to a group or community and are in principle suited to primary or secondary prevention studies in CKDu. A potential limitation of the parallel group cluster design is the number of sites (clusters) required to obtain reasonable balance between treatment or intervention arms (generally at least 6). Stepped-wedge cluster-randomized designs are attractive in that they may require fewer clusters and all groups receive the intervention in a staged roll-out. However, it should be noted that the stepped-wedge design is not suitable for studying disease progression or where the independence of study

outcomes cannot be assumed over the study period. For example, AKI occurring during the control phase may influence the likelihood of AKI occurring in the same individual if they remain in the study during the intervention phase. There is, in short, no one-size-fits-all study design in this unique, incompletely understood condition affecting under-resourced populations.

Given the above challenges, non-randomized intervention study designs are likely to continue to play an important role in developing the evidence base for CKDu [Box 3]. Measures to minimize the potential bias in such studies include a prospective design, randomized recruitment of participants or groups and contemporaneous control group, and collection of sufficient data to permit adjusted analyses that can assess the impact of differences in confounding factors [Box 4]. Regardless of intervention study design, careful assessment of the *implementation* of an intervention is essential. Otherwise, distinguishing between an ineffective intervention and poor implementation can be difficult.[8] Finally, intervention studies should consider incorporating practical and feasible implementation efforts and interventions, and should include economic evaluations to help all stakeholders assess the costs and benefits in light of their own resources and competing community needs. While the added cost of such measures may present challenges, the robust evidence produced becomes a powerful argument for future funding and investment in successful interventions which justifies the initial outlay.

Ethical and cultural considerations

Community, worker, workplace, and health system engagement is vital for CKDu studies to succeed. Consideration must be given to formalizing stakeholder involvement before, during and following the study. Involvement might include an independent consultative committee or the addition of independent members to study steering committees. Researchers must also be cognizant of potential consequences to participating workers who may face economic loss or job insecurity if poor kidney health is identified. A clinical referral plan should be established prior to the start of the study in case adverse health outcomes are identified during the study. Employers or health

policymakers should be engaged to mitigate these consequences. Researchers may convey equipoise for potential for kidney health benefit, but other benefits may nonetheless accrue (e.g., independent of effects on kidney health, safer work practices and/or greater health literacy may yet improve workplace productivity[5] or quality of life). Studies should incorporate secondary outcomes that could demonstrate that investments in community sanitation, water, and healthcare, may have far-reaching benefits, while still allowing a rigorous evaluation of the intervention for CKDu specifically.[9 10] Finally, in keeping with authentic community engagement, researchers should provide results and feedback to participants and communities, local health agencies, workers, and workplaces during and after the study, as well as discuss means of translating findings into an established practice or program.

Conclusions

After two decades of investigation, several plausible hypotheses have been offered to explain the pathogenesis of CKDu, none of which have yet been proven. There is clearly much still to be learned. Given the impact of CKDu on affected communities in these low-resource settings, and the potential benefit from practical interventions, it is critical to develop and execute interventional studies that systematically address suspected risk factors – typically associated with problematic occupational or environmental conditions – and which at the same time, have the power to both contribute to understanding causality of this devastating disease, whilst improving the health of affected or at-risk individuals and their communities at the same time.

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Table 1: Study Design Considerations in CKDu

	Strengths	Weaknesses	Considerations for randomized designs in CKDu
Randomized study structures			
Individual randomization			
Parallel group	• Statistically simple and well-established design	• Participants allocated to control arm do not receive treatment, which may not be possible ethically, nor acceptable to community and participants. • Spread of intervention to control group ('contamination') may be difficult to prevent (especially for behavioral, workplace, or educational interventions).	• Unsuitable when intervention likely to affect the whole study population, or intervention and control individuals likely to share behaviors, information, or treatment (contamination). • Ethical and cultural aspects of randomization need careful consideration in CKDu
Cross-over	• Smaller sample sizes generally required owing to ability to compare intervention and control in same study subject • All participants receive intervention	• As this design cannot be used where a lasting effect of the intervention on the outcome or disease natural history is expected (carry-over effect).	• Unlikely to be of use in CKDu due to carry-over effects. E.g., prevention of incident AKI may affect future susceptibility to AKI, resulting in a carry-over effect that would prevent use of a crossover design. Similar considerations would apply to an educational or behavioral intervention.
Cluster randomized designs			
Parallel group	• Suitable for whole-community or workplace interventions • May permit enrolment of a more representative sample of the population	• Analysis must account for intra-cluster correlation • Cluster trials are statistically less efficient in terms of number of recruited individuals, but this may be outweighed by more efficient implementation of intervention and reduced risk of bias from contamination. • A minimum number of clusters is required (typically ≥ 6 clusters)*	• Ideal design for workplace and community interventions in CKDu, however requirement for multiple sites may present a challenge.
Stepped-wedge	• Greater study power than parallel group cluster study when clusters are heterogenous.	• Statistically more complex with need to account for intra-cluster correlation and for effect of time. • Risk of bias from underlying temporal changes.	• Where cluster members are relatively stable over time (e.g. many workplaces, most communities) one must be able to assume that endpoints occurring in the same individual at different times during the

	• Best suited to study relatively short-term change in incidence of an event.	• As a subtype of cross-over design, stepped-wedge studies are not suited to examine long-term disease progression (e.g. CKD), or where recurrent events within the same pool of individuals is likely (e.g. recurrent AKI within a cohort of workers), as such circumstances may create a 'carry-over' bias.	study are independent. It is unclear how strong this assumption can be for recurrent episodes of AKI in a static population.
Non-randomized (quasi-experimental) designs			
Before-after	• Suitable when few study sites/clusters available • Can be prospective or, given adequate information on the intervention, retrospective • Useful where randomization not feasible/ethical • Lower cost when intervention simple	• Subject to bias due to uncontrolled differences between the before and after periods. • Subject to effect of underlying temporal changes. Trajectory of change in incidence over time can be analyzed for effect of intervention (time-series analysis).	• Prospective before and after studies are preferred. A control period of observation is established prior to introduction of the intervention. This permits standardized outcome ascertainment and a better understanding of any underlying temporal trends.
Non-randomized intervention and control comparisons.	• May be only feasible design when few sites available	• Generate preliminary data, requiring further evaluation. • Subject to bias due to uncontrolled differences between groups	• As far as possible, data collection should be done in the same way across groups. • Detailed information on each group and their exposures/treatments is important to identify potential sources of bias.

***** Minimum cluster requirement varies for each study and is dependent on a statistical power analysis. Most studies are likely to require more than six sites.

Boxes

Box 1: Case study

The Center for Health, Work & Environment (CHWE), Colorado School of Public Health, partnered with a Guatemala-based agribusiness to assess and improve the health, safety, and well-being of their workforce, in particular sugarcane field workers. During the 2016-2017 sugarcane harvest, a Total Worker Health® intervention integrating worker safety with the promotion of health was applied in the form of an education program on the importance of water, electrolytes, rest, and shade along with a "wellness incentive" based on workers' hydration status at the start and end of the work shift. Participants with abnormal kidney function were identified throughout the study and were given additional education and clinical assessments. The researchers observed that dehydration and insufficient electrolyte consumption were risk factors for acute kidney injury across the work shift. In addition, participants identified as having poor kidney health at the start of the study had improvements in markers of kidney health with the intervention, when compared to their trajectories of decline before the intervention over multiple years.

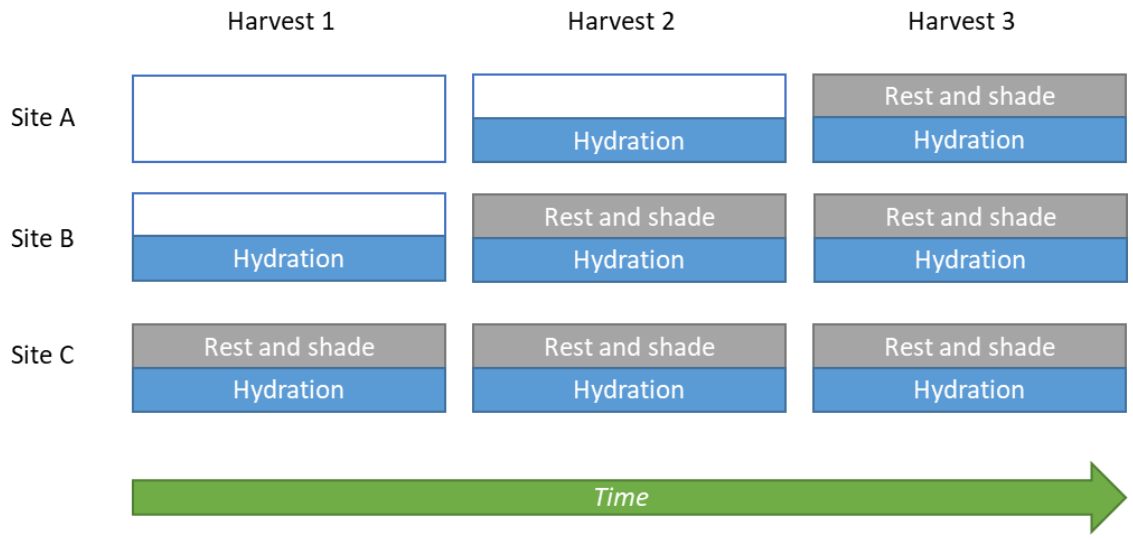
Based on the findings from the intervention study, the agribusiness, in collaboration with CHWE, conducted a 3-week pragmatic comparative effectiveness trial to evaluate impact of electrolyte supplementation on hydration status and health outcomes. Workers received an electrolyte hydration intervention during the 3-week trial. This trial demonstrated the feasibility of maintaining workers' electrolyte levels under extremely hot and humid conditions. With the involvement of the agribusiness' medical team, the study was able to determine that the intervention was achievable and practical to implement. The success of the intervention trial led to a revised hydration program for all field workers in Guatemala, which was rolled-out to the following harvest season.[4]

Box 2: Randomized study in Sri Lanka

In 2017, a parallel group open-label randomized controlled study commenced at the Renal Clinic, Girandurukotte, Sri Lanka. Three hundred and seventy-six people with CKDu were randomized to allopurinol (targeting serum urate levels <6mg/dL in males and <5mg/dL in females) or usual care alone. The primary outcome of this study is change in serum creatinine, with secondary outcomes including hospitalization, cardiovascular events, and need for dialysis. In addition to clinical staff and research assistants, the study also benefits from an existing network of patients' relatives and field health staff who assist in monitoring of adverse effects, as well as facilitating and encouraging participation. Three-year follow up completed in 2021 and results are expected late 2022.

Box 3: Prospective non-randomized study in Nicaragua

The Adelante Initiative is preparing a trial at three worksites in similar geographic and climactic regions. Cane cutters at each site will be followed over three successive harvests, with stepped introduction of a program of hydration and altered work practices designed to reduce the incidence of kidney injury. In year 1, site A will continue usual practice, site B will receive a hydration intervention (provision of water and isotonic beverages), and site C will receive a combined program of hydration and an altered work structure designed to minimize work during the hottest part of the day (with earlier starting times, and frequent scheduled breaks in the shade during working hours). In year 2, site A will receive the hydration intervention, while site B and C will receive the combined program. In year 3, all sites will receive the combined program. Concurrent with this, different implementation support strategies will also be tested by offering intervention training sessions only as opposed to training session plus onsite implementation support in a structured manner through successive harvests. The primary outcome will be episodes of acute kidney injury identified during presentations to local clinics. This stepped-wedge design will test the effect of different aspects of a workplace intervention while ensuring that all groups eventually receive the combined program. With only three sites available, randomization will be unable to meaningfully balance confounding factors, making adjustment for potential confounders an important part of the final analysis plan. This design also permits further demonstration of the hypothesis that heat (and elevated core temperature) *per se* may contribute to kidney injury irrespective of hydration – thus adding nuance to the understanding of CKDu while also potentially finding readily implementable solutions.



Box 4. Key biases in interventional designs

Performance bias - interventions should be applied similarly (adherence) each study site and avoid 'contamination' of control groups by (often well meaning) application of interventions to all participants.

Detection bias - all participants should have their outcome measured in the same manner to avoid biased assessment of outcomes. This includes standard outcome definitions and blinding of assessors wherever possible.

Attrition bias - participants lost to follow up are likely to be different to those who remain in the study, creating a risk of bias due to informative events going unobserved. In occupational health literature, attrition bias includes the 'Healthy Worker Selection Effect' – where injured or ill workers drop out leaving the remaining cohort healthier overall and so potentially decreasing the impact of an intervention.